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Optimising motor learning of infants at high risk of cerebral palsy using goal-oriented and environmental interventions

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Publication Details

Morgan, C. (2015). Optimising motor learning of infants at high risk of cerebral palsy using goal-oriented and environmental interventions (Doctor of Philosophy (College of Medicine)). University of Notre Dame Australia. <http://researchonline.nd.edu.au/theses/113>

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Optimising motor learning of infants at high  
risk of cerebral palsy using goal-oriented and  
environmental interventions

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**Catherine Morgan B App Sc (Physio)**

This thesis is presented for the degree of

*Doctor of Philosophy*

of

The University of Notre Dame Australia

School of Medicine

Supervisors:  
Professor Iona Novak  
Professor Nadia Badawi

June 2015

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## **ABSTRACT**

### **BACKGROUND AND AIMS**

Cerebral palsy (CP) is the most common physical disability of childhood occurring in 1 in 500 live births in developed countries. Although CP starts in infancy because of a lesion in the developing brain, it is usually not diagnosed until about 19 months. The problem with late detection has meant that early neurorehabilitation is not accessed until motor impairment is evident. Consequently the dose of active intervention during the critical period for brain plasticity is often inadequate. Little evidence exists for the effectiveness of early intervention (EI) protocols for infants with CP. In particular, interventions that take a motor learning approach and focus on the task and environment as well as the child, are rarely used. The aim of this research was to evaluate the effectiveness of a motor learning intervention on infants at high risk of CP who were identified early in infancy.

### **METHODS**

A literature review was conducted to explore current practice and evidence regarding how and when CP is diagnosed. Then a systematic review and meta-analysis was carried out to evaluate the effectiveness of environmental enrichment interventions on the motor outcomes of infants with CP. A prospective study assessed the feasibility of detecting CP in an Australian context using the General Movements Assessment (GMA).

An EI enrichment programme “GAME” (Goals, Activity and Motor Enrichment) was then developed based on contemporary motor learning theory and within the framework of family centred practice. GAME was tested in a feasibility 12-week pilot (n=13) and then in a larger (n=30) randomised controlled trial (RCT).

### **RESULTS**

Meta-analysis of five studies demonstrated a small positive effect (SMD=0.39) for environmental enrichment interventions compared to standard care. Accuracy for detecting CP using the GMA was 98% (sensitivity) and 94% (specificity). Results of both RCTs demonstrated an advantage in motor outcomes for infants in GAME at all time points on both norm referenced and criterion referenced outcome measures.

## CONCLUSION

Early identification of infants with CP is possible using evidence based tools. Motor outcomes for infants with CP can be advanced by early and specific motor learning interventions offered in an enriched home environment.

## LIST OF PUBLICATIONS INCLUDED IN THESIS

1. McIntyre S, **Morgan C**, Walker K, Novak I. Cerebral palsy - don't delay. *Developmental Disabilities Research Reviews*. 2011; **17**: 114-29.
2. **Morgan C**, Novak I, Badawi N. Enriched environments and motor outcomes in cerebral palsy: systematic review and meta-analysis. *Pediatrics*. 2013; **132**(3): e735-46.
3. **Morgan C**, Crowle C, Goyen TA, Hardman C, Jackman M, Novak I, Badawi N. Sensitivity and specificity of General Movements Assessment for diagnostic accuracy of detecting cerebral palsy early in an Australian context. *Journal of Paediatrics & Child Health*. 2015. In press.
4. **Morgan C**, Novak I, Dale RC, Guzzetta A, Badawi N. GAME (Goals - Activity - Motor Enrichment): protocol of a single blind randomised controlled trial of motor training, parent education and environmental enrichment for infants at high risk of cerebral palsy. *BMC Neurology*. 2014; **14**: 203.
5. **Morgan C**, Novak I, Dale RC, Badawi N. Optimising motor learning in infants at high risk of cerebral palsy: a pilot study. *BMC Pediatrics*. 2015; **15**(1): 30.
6. **Morgan C**, Novak I, Dale RC, Guzzetta A, Badawi N. Phase 2 single blind randomised controlled trial of GAME (Goals - Activity - Motor Enrichment) in infants at high risk of cerebral palsy. *Submitted to Neurorehabilitation and Neural Repair*.

## PERMISSIONS

Permission has been obtained from relevant journals to reproduce the publications within the thesis. These permissions can be found in the Appendices.

## **Statement of candidate contribution**

### **Declaration of Authorship**

This thesis is the candidate's own work and contains no material which has been accepted for the award of any degree or diploma in any other institution.

To the best of the candidate's knowledge, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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Catherine Morgan

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Date: June 30, 2015

## Statement of Contribution by Others

Contribution of research partners is acknowledged for every publication related to this thesis and is summarised in Appendix B. All co-authors have provided their signatures in Appendix B.

Contributions related to other aspects of the research are listed below:

Intellectual Support:	Professor Nadia Badawi & Professor Iona Novak
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Proposal writing	Professor Iona Novak
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Data Analysis	Professor Iona Novak
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Statistical Support	Professor Iona Novak
---------------------	----------------------

Editorial Assistance	All co-authors as outlined in Author Contributions (Appendix B)
----------------------	---

Financial Support	NHMRC and Cerebral Palsy Alliance Research Foundation Doctoral Scholarship: 1018027
-------------------	---

Cerebral Palsy Alliance Research Institute funded my attendance at two important statistics courses

UNDA provided assistance to present research findings at relevant conferences

Data Collection	Cerebral Palsy Alliance provided “in-kind” support for blind scoring of assessments and specialised equipment for children in the study
-----------------	---

NSW Department of Health assisted in collection of infant assessment and outcome data for study 3

SIGNED:



Prof Iona Novak

Ms Catherine Morgan

## ACKNOWLEDGMENTS

**My heartfelt thanks go to:**

The **families and children** who participated in this research during a very difficult time in their lives.

**Rob White and Cerebral Palsy Alliance** – for building a culture that encourages the pursuit of excellence, real collaboration and making life better than ordinary for people with cerebral palsy.

**Professor Iona Novak** – for encouraging my interest in asking important questions even when they seemed too difficult, for her engagement with all aspects of the project and for being so kind and thoughtful along the way.

**Professor Nadia Badawi** – for being an amazing advocate, taking the time to check in and reminding me that it's all worth doing.

**Associate Professor Karen Walker** - for unprecedented levels of encouragement, practical help with editing and blind scoring assessments.

**Jane Berry, Prue Golland, Salli-Ann Wilson, Dr Petra Karlsson, Dr Monique Hines and Richard Barclay** for helping so cheerfully with blind scoring of assessments.

**Cathryn Crowle, Dr Traci-Ann Goyen, Caroline Hardman, Nadia Reid, Barbara Lucas, and Natasha Carbone** for their tireless help with recruitment.

**Prof Russell Dale and Dr Kristina Prelog** for the hours of time devoted to scoring imaging.

**Dr Andrea Guzzetta** - for blind scoring GMA videos all the way from Italy.

**Professor Roberta Shepherd** - for being such a thoughtful contributor to the field and an inspiration along the way.

My friend **Carla Matthews** - for the fun road trips visiting families, and for taking great videos.

My friend **Dr Sara Denize** - for reminding me that - "this is normal in a PhD".

**Mike and Yvonne Kinch** – for just being so interested and cheering me on. (Sorry you missed the finish line Mike).

**Mum and Dad** – for steadfast encouragement, prayers and practical help.

**Martin, Caleb, Bronte and Isaac** – for WANTING me to do this project, living through a bit of chaos, making all those cups of tea and being very, very patient. Love. Always.

## Platform Presentations During Candidacy

### **Invited presentations**

2014

“Early Detection and Intervention for Cerebral Palsy: Ground-breaking New Tools and Treatments”; American Academy of Cerebral Palsy and Developmental Medicine San Diego, USA; September 2014.

“Optimising Motor Learning in Infants at High Risk of Cerebral Palsy” – International Research Summit on Early Identification and Early Neurorehabilitation, Vienna Austria; July 2014.

“Executive summary: Early Identification and Early Neurorehabilitation in Cerebral Palsy Summit “. European Academy of Childhood Disability, Vienna Austria; July 2014.

“ Early Diagnosis and Early Enrichment for Infants with Cerebral Palsy”; University of Notre Dame Australia, School of Medicine Conference; April 2014

2013

“Early Diagnosis and Early Enrichment in Infants with Cerebral Palsy” – CP Alliance Research Foundation Briefing, October 2013.

“Early Identification of Cerebral Palsy” – International Research Summit; Neonatal Encephalopathy and Hypoxic Ischaemic Encephalopathy: Advancing the Science and Improving Outcomes; Washington DC, 2013.

“ Intervention in CP: state of the evidence”; United Cerebral Palsy Conference; San Diego USA, April, 2013

“Movement Disorders”, workshops; Auckland and Christchurch New Zealand, May 2013.

Papers and Workshops presented with published abstracts

2014

Morgan C, Novak I, Badawi N. "Effectiveness of Environmental Enrichment on Improving Motor Outcomes of Infants at High Risk of Cerebral Palsy: Systematic review and Meta-Analysis". Hunter Valley Australia: Australasian Academy of Cerebral Palsy and Developmental Medicine

Morgan C, Novak I, Badawi N. "Environmental enrichment utilizing motor learning enhances motor outcomes of infants at high risk of CP: randomised controlled trial pilot study". Hunter Valley Australia: Australasian Academy of Cerebral Palsy and Developmental Medicine

Morgan C, Novak I, Badawi N. "Game On: Goals and motor enrichment for infants with CP". Hunter Valley, Australia: Australasian Academy of Cerebral Palsy and Developmental Medicine

Novak I, Morgan C, Badawi N, Goyen TA, Hardman C, Crowle C. "Sensitivity and specificity of general movements assessment for detecting cerebral palsy in an Australian context". Hunter Valley Australia: Australasian Academy of Cerebral Palsy and Developmental Medicine

Morgan C, Novak I, Badawi N. "Optimizing motor learning of infants at high risk of CP: randomised controlled pilot study". San Diego USA: American Academy of Cerebral Palsy and Developmental Medicine

Novak I, Morgan C, Wallen M. "Effective Evidence-Based Therapy for Children with Cerebral Palsy". San Diego USA: American Academy of Cerebral Palsy and Developmental Medicine.



2012

Campbell L, Craik S, Dark L, McIntyre S, Morgan C, Morton N, Novak I, Stumbles E. "Meeting of the minds: Knowledge translation alliances between decision-makers, knowledge brokers and researchers for maximising client outcomes". Brisbane Australia: Australasian Academy of Cerebral Palsy and Developmental Medicine

Novak I, Karlsson P, Smithers-Sheedy H, Morgan C, et al. "Measuring What Matters in CP : How surveillance can benefit clinical practice". Brisbane Australia: Australasian Academy of Cerebral Palsy and Developmental Medicine

Morgan C, Novak I, Badawi N. "Effectiveness of Environmental Enrichment on Improving Motor Outcomes of Infants at High Risk of Cerebral Palsy: Systematic review and Meta-Analysis." Pisa, Italy  
Fourth international Cerebral Palsy Conference

## LIST OF ABBREVIATIONS

Abn F	Abnormal fidgety
ACPR	Australian Cerebral Palsy Register
AHEMD –IS	Affordances in the Home Environment for Motor Development – Infant Scale
BGT	Basal ganglia/thalamus
BSID-III	Bayley Scales of Infant and Toddler Development – third edition
cPVL	Cystic periventricular leucomalacia
CIMT	Constraint Induced Movement Therapy
CM	Cathy Morgan
COPM	Canadian Occupational Performance Measure
CP	Cerebral palsy
CUS	Cranial ultrasound
CS	Cramped synchronised
DASS 21	Depression, Anxiety, Stress Scale - short version
EI	Early Intervention
F-	Absent Fidgety
GAME	Goals, activity, motor enrichment
GAS	Goal Attainment Scale
GDT	Goal directed training
GMs	General Movements
GMA	General Movements Assessment
GMFCS	Gross Motor Function Classification System
GMFM- 66	Gross Motor Function Measure – 66
HIE	Hypoxic ischaemic encephalopathy
HOME	Home Observation for Measurement of the Environment
HP	Home programme
ICF	International Classification of Functioning, Disability and Health
IN	Iona Novak
IVH	Intraventricular haemorrhage
MRI	Magnetic Resonance Imaging
NE	Neonatal encephalopathy
NICU	Neonatal Intensive Care Unit
PEDro	Physiotherapy Evidence Database
PDMS-2	Peabody Developmental Motor Scales – Second Edition
PR	Poor repertoire
PVL	Periventricular leucomalacia
RCT	Randomised Controlled Trial
SC	Standard Care
SCHN	Sydney Children’s Hospital Network
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
RevMan 5	Review Manager 5
WMI	White matter injury



## **Chapter 1: INTRODUCTION**

### **1.1. The problem: How to optimise the motor development of very young infants with or at the highest risk of cerebral palsy**

#### **1.1.1 Cerebral Palsy**

Cerebral palsy (CP) is the most common physical disability of childhood affecting 34,000 Australians with approximately 700 new cases diagnosed each year. The current definition of CP is “a group of disorders of the development of movement and posture, which are attributed to non-progressive lesions of the developing fetal or infant brain” (1). The motor impairments of CP are variable and range from a mild to severe and may be unilateral or bilateral, affecting all limbs, the trunk and neck. Consequently the activity limitations of CP are also variable and the condition is considered highly heterogeneous. The heterogeneity of CP is suggested in the definition (“group of disorders”) and is evident in the variation in antecedents, motor ability, the predominant motor patterns of CP, and the presence of secondary impairments that are frequently co-occurring in CP.

The Gross Motor Function Classification System (GMFCS) is a universally used system that classifies CP according to level of motor function (2). Children in levels I and II walk independently and according to CP Register data account for 60% of all CP (3). Children at level III ambulate with assistive devices and often become non-ambulators in adolescence (4). Those classified as levels IV and V are wheelchair dependent where independence in operating a wheelchair and the ability to weight-bear for transferring are often the separating factors between levels. Children in levels GMFCS IV and V account for 30 % of all CP (3). Manual ability has also been classified for children over four years of age with the Manual Ability Classification Scale (5)

CP can also be described by the predominant type of movement disorder, with spasticity the most common form (85-90%) followed by dyskinetic CP (4-7%) (6). Many people have a mixed presentation with either spasticity or dyskinesia as the predominant disorder.

In addition to motor difficulties, a diverse range of secondary impairments often accompanies CP. A recent systematic review found that 3 in 4 people with CP experience pain, 1 in 4 are non-verbal, over 40% have a cognitive impairment and 1 in 4 have a vision impairment (7). In addition secondary impairments may arise as a result of the “natural history” of CP leading to debilitating contractures and joint deformity and a functional decline in motor ability (4).

### **1.1.2 Therapeutic Interventions for CP**

Rehabilitation interventions are the standard of care for children with CP, and available interventions broadly fall into 3 categories; (i) those that aim to improve function; (ii) those that aim to prevent secondary impairments from occurring; and (iii) those that provide compensation by adapting the environment around the child (6). A number of systematic reviews demonstrate that high quality evidence exists for some interventions that aim to improve motor function in children with CP including constraint induced movement therapy (CIMT), bimanual training, goal directed training and goal oriented home programmes (8). However there are still many interventions with poor supporting evidence that are part of the standard care of children with CP. The lack of evidence is in part due to difficulties in conducting studies of high methodological quality with children of heterogeneous conditions. Indeed many of the intervention studies that have been shown to be effective are of more homogenous samples, for example hemiplegia (9). The heterogeneity of CP is increasingly thought to be a significant contributor to the difficulties encountered when studying interventions for this diverse group of people (10).

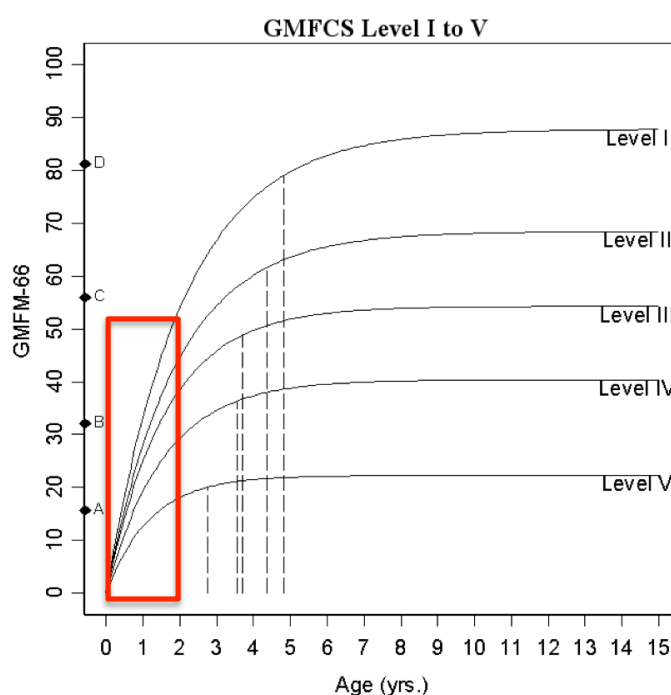
### **1.1.3 Motor Trajectories in CP**

Typically developing children display a relatively predictable sequence of motor milestone acquisition although there is some variation in age of attainment (11). During the first year of life infants learn to sit, crawl on hands and knees, stand with assistance and about 50% walk unassisted by their first birthday. Concurrently, infants are developing increasingly complex reach and grasp

behaviours and by 12 months are able to use both hands to reach for, transfer and grasp and release objects

The heterogeneity of CP in terms of motor function has been well described in a landmark study in 2002, the Ontario Motor Growth Study. Individual scores on the Gross Motor Function Measure were mapped against age and stratified by GMFCS levels to create motor development curves for CP (12). These curves are useful for predicting likely mobility outcome and are widely used as a tool to discuss prognosis with families as well as plan realistic rehabilitation goals. The study and resulting gross motor curves demonstrated that children with CP achieve 90% of their gross motor development potential by age 5 across all GMFCS levels, after which a plateauing effect occurs. Children at GMFCS level V reach this point before 3 years of age (Figure 1).

Figure 1: Steepest portion of CP Motor Curves (Figure used by permission from JAMA)



This graph shows the observed and predicted GMFM-66 scores for children in GMFCS Levels I through V. The curved solid lines indicate average performance. The horizontal dotted lines on the right of the figures indicate the band expected to encompass 50% of children's limits of development. The solid vertical lines indicate the average age-90 (the age in years by which children are expected to reach 90% of their motor development potential). The dotted vertical lines indicate the bands expected to encompass 50% of age-90 values around the average. The absence of 50% bands in level IV and level V indicates low variation in age-90 values.

JAMA 2002; 288:1357-63. Copyrighted 2002, American Medical Association

As would be expected, the steepest portion of the curves occur between 0 - 2 years although in this large cohort study only 68 of the 657 children (10%) were between one and two years of age. Infants under one are not reported in this study. In other words, very little is known about the motor trajectory of infants with CP before the age of two. Tabulated reference percentiles are available for children from two years demonstrating the great variance even within GMFCS levels (13). There are no equivalent curves for infants and toddlers.

Infants with brain lesions usually have slower motor development than their age matched peers due to the impaired development of sensorimotor pathways and their target structures (motoneurons and muscle) (14). The location and extent of the brain lesion is one of several factors that predict outcome severity in children with CP. White matter injuries (WMI) are the most common type of injury accounting for up to 46% of all CP (15). About two thirds of infants with WMI will have milder motor impairments (GMFCS I-II) with hemiplegia and diplegia the more common motor distribution types. Cystic periventricular leukomalacia (cPVL) is often associated with non-ambulant CP especially when it is bilaterally distributed and occupies more than 5% of the hemispheres (16). Grey matter lesions occur in about 25% with hemiplegia the most common outcome (17). Hypoxic Ischaemic Encephalopathy (HIE) can lead to mild or severe outcomes with injuries to the basal ganglia and thalamus often leading to dyskinetic CP affecting all limbs. Where injury only involves the white matter motor disability may be milder (18). Similarly maldevelopment of the brain can result in severe motor and cognitive disability or mild motor dysfunction (19). Although the degree and location of damage to the motor areas of the brain is predictive of outcome, associated impairments such as cortical vision impairment, cognitive delay and uncontrolled epilepsy also impact on motor development and function.

#### **1.1.4 Early Intervention evidence in CP**

Not only is little known about the motor trajectories of infants with CP, the early intervention literature for CP is also problematic. Good evidence exists for the effectiveness of interventions for older children with CP that take a goal-

oriented and motor learning approach to therapy (8). Studies in both children with CP and adults with acquired brain injury have demonstrated that the repeated practice of task – specific activities leads to improvements in gross motor function and performance of daily activities (20-22). Evidence in the field of early intervention in CP is far less convincing. A recent search of the Cochrane Database of Systematic Reviews and Physiotherapy Evidence Database (PEDro) over the last 10 years identified 6 systematic reviews (23-28) evaluating child-focused early intervention programmes for infants 0 - 2 at high risk of CP (Table 1). Of these systematic reviews four focus only on preterm infants, and only two specifically evaluate the impact of early intervention on infants with CP. One of these is paper 2 of this thesis (28). A great deal of variability exists in programmes typically offered to high risk infants and although cognitive and social gains have been shown in studies of preterm infants, motor gains are generally not found. Even cognitive gains are generally not maintained after intervention ceases (27).

The main types of interventions that have been studied in infants for the purpose of advancing motor development vary and include Neurodevelopmental Therapy (NDT) (29), general developmental stimulation, developmental skills approach (30) and conductive education (31). To date there is little evidence to show that motor outcomes can be influenced significantly by any of these approaches over and above what is expected from natural development (32).

TABLE 1: Systematic reviews evaluating child focused interventions in children 0-2 years (2005-2015)

CITATION	POPULATION	INCLUDED INTERVENTIONS	MOTOR OUTCOMES	NON-MOTOR OUTCOMES
<b>Benzies et al;</b> <b>2013</b> <sup>(23)</sup>  <b>SR and MA</b>	Preterm	Various programmes that included parents	Not reported	Significant positive maternal depression,



				anxiety and self efficacy
<b>Blauw-Hospers et al; 2005<sup>24</sup></b>	Preterm At risk of disability CP	Various programmes aiming to improve motor development	Mixed results NDT ineffective Specific and general programmes might have beneficial effects depending on age of infant	Mixed results
<b>Fernandez et al; 2012<sup>25</sup></b>	Preterm infants	Physiotherapy intervention programmes	Mixed results; studies heterogeneous	Not reported
<b>Schulzke et al; 2014<sup>26</sup> SR and MA</b>	Preterm infants	Physical activity programmes	Not reported	Positive effect on weight gain and linear growth
<b>Spittle et al; 2012<sup>27</sup> SR and MA</b>	Preterm	Various child oriented programmes	Small effect in short term	Significant positive cognitive
<b>Morgan et al; 2013<sup>28</sup>  SR and MA (Paper 2 of this thesis)</b>	CP/high risk of CP	Programmes including an environmental enrichment component	Small positive effect at end of treatment period	Not reported

SR= systematic review; MA=meta-analysis

### 1.1.5. Diagnosing CP

One of the key reasons for the paucity of EI trials for infants with CP relates to age of detection of CP. A problem with many EI trials aiming to recruit infants with CP is that they unintentionally end up with a mixed group including some participants with mild motor dysfunction, some with normal outcomes and only a few with CP. For example, although premature infants are regarded as “high-risk” only 10% or less will go on to have CP making it difficult to generalise findings from the high number of studies of this population (3). Underpowered trials for CP are the consequence of late detection.

Although CP results from an injury to the developing brain (i.e. occurs in infancy) a formal diagnosis is often not made until the second year of life. In Australia the average of diagnosis is 17 months for children who were monitored closely after birth as well as for those who present with motor delay during late infancy (unpublished data from Australian Cerebral Palsy Register). Only infants with a history of neonatal encephalopathy are diagnosed earlier, at an average of 13 months. Confirming a diagnosis of CP is typically a complex process. When infants are closely monitored because of neonatal risk factors such as prematurity or encephalopathy, motor delays might be noted earlier although a “wait and see” approach is often preferred (6). The chance that an identified brain injury might not lead to the activity limitations necessary for a CP diagnosis leads practitioners to be cautious. For children with no apparent risk factors, investigations typically begin when it becomes apparent that motor milestones are not being reached, in particular sitting or standing. However as many standardised motor tests are not specifically predictive of CP (33) and some “tell-tale” motor signs such as spasticity do not appear until the second year, it can still be some time before an official diagnosis is given. Before making a diagnosis, medical professionals wish to rule out other potential conditions (34) and ensure the condition is not progressive. Brain imaging is widely used to document the presence and extent of injury and increasingly sophisticated tools are under development (35). However, clinical research also documents outcomes that do not seem to “match” imaging findings (36) and up to 15% of children with CP have normal neuroimaging. Nevertheless, a number of

systematic reviews have demonstrated that certain defined patterns of injury in the grey and or white matter nearly always lead to CP indicating the importance of appropriately timed neuroimaging in the diagnostic process (15,16,18,37).

Prechtl's Qualitative Assessment of General Movements (GMA) (38) a diagnostic observational tool, has been shown to be predictive of neurological outcome, particularly CP, in high- risk preterm and term-born infants. Spittle and colleagues demonstrated a correlation between abnormal GMs and abnormal white matter and suggest that a combination of GMs assessment and structural MRI in high-risk infants is a logical approach to early detection of CP (39). Despite numerous publications and high quality systematic reviews this approach to early detection is still not commonly used (38). Published algorithms for diagnosing CP do not include GMA and recommend neuroimaging when tone is assessed as high (34). The combined use of GMA and appropriately timed neuroimaging is a potential solution to the problem of late detection.

Standard of care for infants at high risk of CP includes in the first instance, frequent monitoring, and early intervention (EI) if motor delay appears to be worsening. Accessing EI however, can be dependent on a confirmed diagnosis or a sufficient description of "at risk " status. There is a growing body of research indicating that this period of time is the critical window of infant brain development. An increasing amount of neuroscience literature demonstrates that perinatal damage to the developing corticospinal tract is worsened by inactivity (41). Martin and colleagues found in a cat model of CP, that activity based therapies delivered early, re-established corticospinal connections and led to improved control of the affected limbs (42). In humans the first 18 months of life are considered critical for development of the corticospinal tracts (42, 43). Theoretically, infants with brain injuries affecting the motor regions of the brain ought to respond best to active interventions applied as early within this critical window as is possible.

The tendency for late diagnosis, coupled with service dependent diagnostic criteria, creates a problem for timely access to interventions that aim to optimise

the neural organisation occurring during this time period. Additionally once infants are referred, the model and type of service provision to these children is variable. A recent intervention study in the US found that the variation in standard care for high risk infants varied enormously with more than 50% of participants in the study unable to access physical therapy intervention before 12 months of age (44).

We hypothesised late detection and thus low dose early intervention was standard of care (described in chapter 7) in our region. In a survey of NICUs in Sydney in 2011, prior to the implementation of GMA in most NICUs, we found that the average amount of EI received by an infant at high risk of CP in the first year of life was only 14.2 hours (survey questions and table of outcomes listed in appendix 1). Moreover, the inclusion criteria for follow up post discharge varied from site to site. Some had no standard follow up for infants with HIE for example, whereas others followed all infants with HIE until early childhood. It seems likely that a proportion of infants at high risk of CP might be “slipping through the cracks” despite the existence of follow up services.

#### **1.1.6 Neuroplasticity and motor function**

It is the intrinsic ability of the brain to change and organise itself that provides the scientific background to the purported benefits of rehabilitation. Neuroplasticity has been the subject of both basic science and clinical research for several decades. Demonstrable changes in structure, function and connections at the molecular and cellular level provide scientists and clinicians with confirmation that injuries to the brain are not static and that exploiting these mechanisms might be the solution to recovery. The search for interventions to harness neuroplasticity mechanisms is ongoing in many fields (45). A number of studies have investigated the place of pharmacological interventions in animal models (46) or repetitive Transcranial Magnetic Stimulation in changing the levels of excitability in the corticospinal tract (47). Clinically feasible rehabilitation protocols aim to harness activity - dependent plasticity mechanisms by providing repetitive experience to retrain functional skills lost as a result of injury. Adult stroke studies have demonstrated changes

in neural organisation as a result of motor training, for example studies of CIMT have demonstrated structural neuroplastic change (48). Researchers and clinicians in the rehabilitation field want to know the type and intensity of clinically feasible strategies that can be used to promote optimal neural organisation. Allied health professionals providing interventions to infants with CP urgently need evidence based protocols that are grounded in neuroscience.

At the same time as advances in neuroscience have been progressing, the focus of developmental research has shifted from a neuro-maturational framework, sometimes referred to as “disembodied development”, to one of an interaction of multiple dynamic systems or “embodied development” (49, 50). In these contemporary frameworks purposeful motor behaviours are understood to emerge from a convergence of child-specific (biomechanical and physiological), task-specific and environmental constraints and processes. A variety of novel and ground-breaking experiments have shaped our understanding of how normal motor development progresses and ought to form the basis of motor intervention programmes. Some of these findings are listed below:

1. **Biomechanical factors** influence motor development at a very young age. Thelen demonstrated over 30 years ago that the loss of the stepping reflex was attributed not to increasing supraspinal inhibition, the prevailing assumption of the day, but increasing body mass rendering the infant’s leg muscles too “weak” to lift the legs against gravity (51). Thus “practice” of stepping maintained muscle strength and led to earlier walking and retention of the stepping reflex, an observation that had previously been attributed solely to the effects of neuromaturation (52).
2. Infants who are developing typically learn by **trial and error** and display high levels of variability in movement solutions for achieving a motor goal (53).
3. **Task constraints** influence the emergence of motor skills. Studies by Fetters and colleagues showed that by simply changing the weight of a mobile positioned for kicking, both the frequency and pattern of kicking behaviours could be altered in infants as young as 4 months of age (54).

4. *Environmental factors* influence the rate and trajectory of motor development. Child rearing practices across different cultures (55) and parent training of specific motor activities have been shown to advance the emergence of motor skills (56-57).

5. *Intensity of practice* is a determining factor in the rate of motor development. A study examining the characteristics of the emergence of walking postulated that the amount, variability of and distribution of practice were crucial factors in the successful development of walking (56). Repetition is a key principle of motor learning.

“Dynamic systems” provide the theoretical background to evidence based motor learning interventions for children with CP including goal - directed training (GDT) or functional training (59). This approach uses mutually agreed upon, meaningful goals to shape the intervention plan. Then aspects of the desired goal are considered in relation to child-specific (for example muscle strength), task specific (task analysis is used to “break down” the task into components), and environment specific characteristics. Frequent repetitive task practice is a key component of this intervention and a coaching framework may be used with children of suitable age and cognition (60). To date, the application of GDT has demonstrated positive results in older children with cerebral palsy and adults with acquired brain injury however there have been no published studies using this approach in young infants with CP. Goal oriented interventions for infants at high risk of CP that utilise principles of motor learning could be a potential solution for advancing the motor trajectories of these children during the critical neuroplastic window.

#### **1.1.7 Enriched environments**

The study of Enriched Environments (EE) has been proven to enhance neuroplasticity in animal studies and in adults with neurological disorders. Gains documented include improved memory and motor recovery (61). Environmental enrichment is arguably a potential rehabilitation “solution” for those with brain injuries and studies of the contribution of EEs to recovery after adult stroke are underway (62). While animal studies use consistent animal

housing set-ups, it is more difficult to describe the “essential ingredients” of an enriched environment in human rehabilitation settings. It seems in the human context more is known about deprivation and its negative consequences than is known about enrichment (63). Multiple studies of “at risk” children, most notably premature infants and those from low socioeconomic groups, have examined the value of enrichment in enhancing outcomes. These studies demonstrate significant benefits in cognitive and behavioural development via the enrichment of either home or day care environments, or from a variety of early intervention programmes that aim to enhance the child’s learning environment (64, 27).

The home environment has for many years been recognised as a key-contributing factor to favourable outcomes for children at risk. The International Classification of Function and Disability (ICF) also highlights the importance of environmental factors in influencing activity and participation of children with disabilities (65). Maternal mental and physical health and confidence, sleep, child rearing practices, socioeconomic factors (66) and support networks are all regarded as important contributors to child health and development (67). In fact, the home environment is considered so crucial that service delivery frameworks that are family centred are now considered standard of care in early intervention and child rehabilitation programmes (68). Family Centred Practice recognises the family as the constant in the child’s life and that families are invaluable partners to health professionals. Family centred care aims to enhance the competencies of the family in their care giving role.

Early Intervention programs for infants who are at risk of poor developmental outcomes aim to enrich the child’s environment. These programmes tend to be home based, educational in nature and rely on the parents/ carers to provide the interventions with the support of various professionals (69,70). Recent systematic reviews have demonstrated that although home -based early intervention programs for infants regarded as “at risk” are the norm, a positive impact on motor development is yet to be clearly demonstrated (24,27).

## **1.2 Research Questions**

The thesis brings together a series of papers investigating the feasibility of detection of CP early in infancy and the effectiveness of environmental enrichment and early motor learning interventions on the motor outcomes of young infants at high risk of CP. This research addresses the following questions:

- Is it possible to detect CP early in an Australian context?
- If it is possible to detect CP early, then at what age can it be detected and what are the best tools to accurately identify CP in infancy?
- How effective is early intervention for improving motor outcomes of infants with CP?
- Does environmental enrichment influence the motor outcomes in infants with CP?
- Can motor learning interventions effective in older children with CP be implemented for infants with CP or who are at very high risk of CP?
- Does a home-based, goal oriented rehabilitation approach that educates and supports parents to practice motor tasks with their baby lead to improved outcomes for infants with CP?

## **1.3 Aims of research**

In response to the research questions, the aims of this thesis are:

1. To review the literature regarding the early detection of CP
2. To review the evidence for the effectiveness of interventions aimed at enriching the environment of infants with CP or at high risk of CP
3. To assess the sensitivity and specificity of the General Movements Assessment for detecting CP in infants 3-4 months of age in an Australian context
4. To develop and describe the content of a goal oriented motor learning intervention that combines environmental enrichment, intensive motor



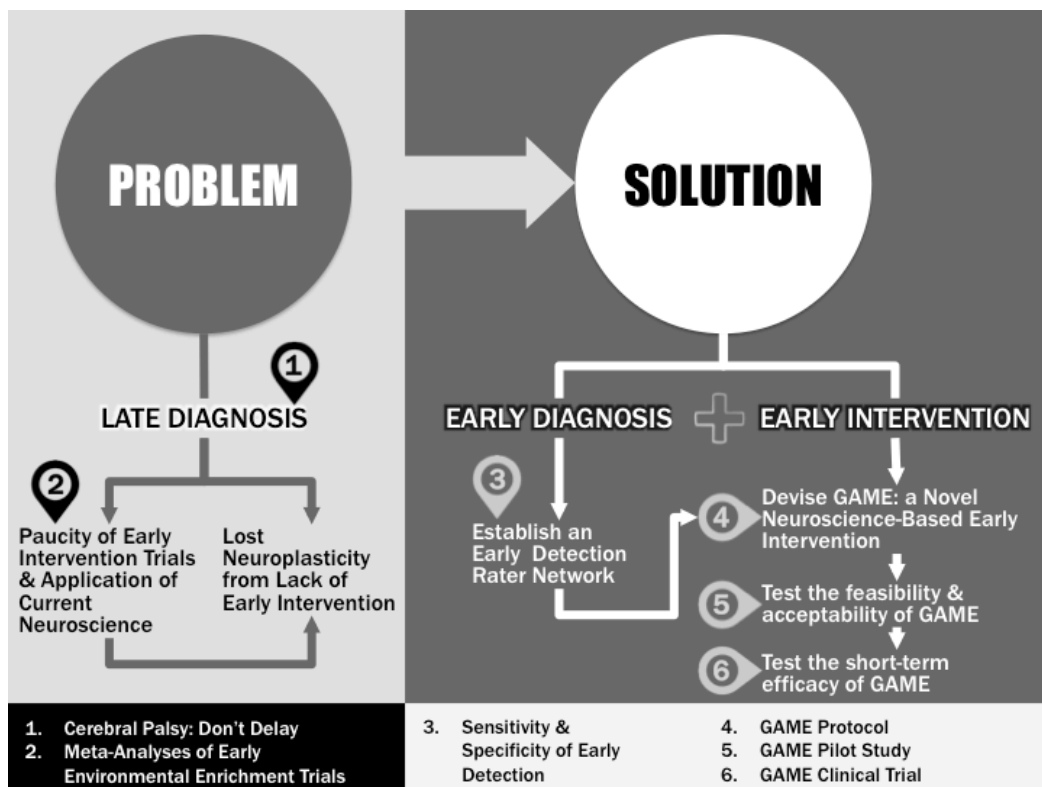
training and parent education called GAME (Goals Activity and Motor Enrichment)

5. To test the feasibility of early detection of CP using the GMA to recruit infants to a pilot RCT of GAME intervention and to test the outcomes of GAME after 12 weeks of intervention compared to usual care
6. To test the efficacy of GAME in a larger RCT on motor outcomes in the short and longer term

#### 1.4 Outline of studies

An outline of the studies and how they fit together in this thesis is portrayed in Figure 2. In the first 2 studies the problem and consequences of late diagnosis of CP is discussed. The paucity of evidence for the effects of EI for infants with CP is a product of a lack of a systematic approach to early detection and the dearth of intervention protocols based on basic science and of effective rehabilitation strategies that work in older children with CP.

Figure 2: Diagrammatic representation of the studies



The solution to this problem is the subject of the remaining studies. Study 3 represents the result of a knowledge translation project that was coordinated to embed the use of the GMA into clinical practice. A rater network was established and infant assessment and outcome data collected across 5 recruitment sites. The sensitivity and specificity of the GMA for detecting CP in this Australian rater network is detailed.

Studies 4-6 describe the aims, methods and results of a novel EI approach for infants at high risk of CP. The intervention, GAME (**G**oals – **A**ctivity – **M**otor-**E**nrichment), is described and tested in both a small (phase 1) pilot study and then in a larger (phase 2) RCT.

The final chapter draws together the findings and limitations of the study and discusses future directions for research in the field.

#### **Study 1: (Chapter 2)**

Aim 1: To review the literature regarding the early detection of CP

A literature review was conducted to describe the risk profile of CP in neonates and to identify the assessment tools with the highest predictive capacity to detect CP in infancy.

Results 1: High level evidence exists that CP can be detected early

#### **Study 2: (Chapter 3)**

Aim 2: To review the evidence for the effectiveness of interventions aimed at enriching the environment of infants with CP or at high risk of CP

A systematic review was undertaken to summarise the evidence of the effectiveness of environmental enrichment interventions in infants with CP. In the absence of a formal definition of environmental enrichment for humans, a working definition based on animal literature is proposed. A meta-analysis combines data from five studies that compared environmental enrichment interventions with standard care.

Results 2: A small positive effect on motor outcomes exists for the benefits of interventions including environmental enrichment compared to standard care.

### **Study 3. (Chapter 4)**

Aim 3: To assess the sensitivity and specificity of the General Movements Assessment for detecting CP in infants 3-4 months of age in an Australian context.

A knowledge translation project was conducted to enable early detection of CP. A targeted training programme in Prechtl's Qualitative Assessment of General Movements in Sydney's Neonatal Intensive Care Units was undertaken. Data collected from five sites over a 30-month period was analysed to determine if sensitivity and specificity of detecting CP in 3-4 month old infants was comparable to internationally published rates.

Results 3: Diagnostic accuracy for detecting CP using the GMA was comparable to international rates with a sensitivity of 98% and specificity of 94%.

### **Study 4. (Chapter 5)**

Aim 4: To develop and describe the content of a goal oriented motor learning intervention that combines environmental enrichment, intensive motor training and parent education called GAME (Goals Activity and Motor Enrichment)

A clinical protocol for a goal-directed, intensive motor training intervention (labelled GAME) in infants was devised, based on published literature.

Results 4: After it was tested in a small pilot (study 5) the protocol for a larger RCT (study 6) was developed and published.

### **Study Five: (Chapter 6)**

Aim 5: To test the feasibility of early detection of CP using the GMA to recruit infants to a pilot RCT of GAME intervention and to test the outcomes of GAME after 12 weeks of intervention compared to usual care.

The GAME protocol was tested in a small pilot study. This pilot aimed to test both the feasibility of the recruitment and randomisation strategies as well as the acceptability of the intervention to parents. Outcome data from the pilot study were used to conduct a power analysis for the randomised controlled trial, to ensure the study had adequate sample size to detect change if present.

Results 5: Twelve weeks of GAME intervention resulted in favourable motor outcomes compared to standard care. The intervention was clinically feasible to do and recruitment and randomisation procedures were acceptable to all stakeholders.

### **Study Six (Chapter 7)**

Aim 6: To test the efficacy of GAME in a larger RCT on motor outcomes in the short and longer term

A single blind randomised controlled trial (RCT) with 2 groups was used to evaluate whether improved motor outcomes in infants with (CP) result from GAME OR standard care. Results are reported after 16 weeks of intervention and at one year.

Results 6: Between-group differences favouring GAME intervention were found in motor skills after 16 weeks of intervention. Furthermore, at 12 months corrected age, GAME participants had significantly higher motor function and cognition scores compared to standard care.

## **1.5 Significance of the research**

In Australia, 700 new cases of CP are diagnosed each year. By 2050 there are expected to be over 47, 000 people living with CP in Australia. CP is more

common in any year than the most common types of cancer, stroke and road traffic accidents and is in the top five most costly conditions on a per capita basis of 15 conditions studied by Access Economics in recent years (68). The cost of CP was estimated at 1.47 billion in 2007, and 43% of this cost is borne by individuals with CP and their friends and families, and is almost certainly an underestimate. The recent introduction of the National Disability Insurance Scheme in Australia will see costs for services for people with CP continue to rise with more of the financial burden falling to government. Evidence based interventions are important not only to minimise the impact of CP on the quality of life for children and their families but also to assist government and policy makers to allocate resources and efforts to programmes shown to be effective. The findings of this research have the potential to improve the outcomes of these children by reducing the age of detection of CP thus allowing early access to intervention. This study is unique because previous interventions with this population either (a) started late i.e. outside the optimal neuroplastic window, because of a “wait and see” method of diagnosis; or (b) utilised a normalisation of movement approach for example, Neurodevelopmental therapy (NDT), which have been shown to be ineffective. This research makes a unique contribution to advancing knowledge about early intervention for infants at high risk of CP because it instead tests the effectiveness of proven effective interventions in older children in this younger population. Since motor learning interventions have not been tested in very young infants it is still unknown if severity of impairment can be minimised by taking advantage of neuroplastic mechanisms very early in life using activity based protocols such as those contained in this research programme.

## **1.6 Ethics**

Ethical approval was obtained from the Human Research Ethics Committees of the Children’s Hospital at Westmead, the University of Notre Dame Australia, Cerebral Palsy Alliance and Royal Prince Alfred Hospital (appendix a). The larger RCT was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12611000572965) in 2012.

## **1.7 Funding Support**

The conduct of these studies was funded via doctoral scholarship co-funded by the National Health and Medical Research Council (NHMRC) and the Cerebral Palsy Research Foundation (1018027).

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## APPENDIX 1:

### Survey questions:

1. When an infant is discharged from the NICU is high risk of CP discussed?
2. What is the routine follow up plan? Is it related to birthweight, medical conditions or gestational age?
3. At what ages are they followed up and by whom?
4. What assessments do they have and at what ages?
5. Are they referred to allied health? Who/where/why? What is frequency of intervention?
7. What is the usual age for a definitive diagnosis of CP to be given

NICU	Follow-up inclusion criteria	Diagnostic window	Follow up time points	Timing of allied health referrals	Intensity of allied health interventions if referred
1	Gestational age: < 30 weeks Growth restriction: <37 weeks + on 3 <sup>rd</sup> centile Neuro: HIE OR other neurological concern	Inpatient: Initial discussion of "high risk" Follow up: Final diagnosis by 12 months at latest	6 weeks 4, 8 and 12 months 3, 5 and 8 years	Varies: Often 4 or 8 months as determined by clinic staff	Can vary from follow up to monthly or fortnightly for infants; less intense if older
2	Gestational age: <32 weeks Growth restriction: sometimes Other: complex	Inpatient: Risk discussed prior to discharge Follow up:	4, 8 and 12 months Up to 3 years if < 29 weeks	Varies: At any follow up time point as assessed by NICU	Individualised; no parameters given

	medical needs	Final diagnosis by paediatrician between 1-3 years		allied health staff	
3	Gestational age: <29 weeks, Weight: <1000g, Neuro: Grade 3 or 4 IVH, PVL, seizures, meningitis Other: protracted hyperglycaemia	Inpatient: Risk discussed more than once Follow up: Final diagnosis ranges from 4 months (severe CP) - 2 years (mild CP)	4, 8 and 12 months 2 and 5 years if <750 gram or <27 weeks	Varies – at discharge in some cases or at any follow up time points if abnormal or delayed development noted	Monthly to fortnightly for infants Less frequent for toddlers
4	Any baby at risk of developmental delay who is not followed up by another service (eg cardiac follow up)	Inpatient: Discussion based on test results re “high risk” Follow up: Final diagnosis given between 6 months- 3 years	4 and 12 months and 3 years  If concerned also 8 and 18 months	Varies – at discharge in some cases or at any follow up time points if abnormal or delayed development noted	Monthly on average



5	Gestational age: <29 weeks, Weight: <1000g, Neuro: grade 3 or 4 IVH or specific risk factors such as seizures	Inpatient: General discussion of "High risk" category Follow up: Final diagnosis 6-12 months or later if mild	1,3,4,6,8,1 2 and 18 months (physio) 1, 2, 5 and 8 years (medical)	Physiotherapy for all high-risk group, seen at the hospital.	Monthly – every 2 months however more intense block of weekly to fortnightly may be offered for a short period
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## Chapter 2 | Study 1 “ CP - DON'T DELAY”

### PUBLICATION

McIntyre S, **Morgan C**, Walker K, Novak I. Cerebral palsy - don't delay. *Dev Disabil Res Rev*. 2011; **17**:114-29

This first paper provides a narrative review of the difficulties of diagnosing CP and gives a rationale regarding the importance of the early detection of CP. The paper outlines the difficulties of applying diagnostic labelling to a condition known as an “umbrella term” in the absence of readily available biomarkers.

The concept of “high risk of CP” is discussed with reference to premature infants, term infants with neonatal encephalopathy and term infants with no apparent risk factors who later go on to be diagnosed with CP. Data indicated that it is possible to find and therefore study these infants early to advance the early intervention evidence base.

The assessment tools with the highest predictive power for CP are summarised, enabling recommendations to be made that aim to:

1. Enable earlier and accurate diagnosis of CP for high-risk infants
2. Provide an evidence based care pathway for children born preterm or term and at high risk of CP
3. Facilitate earlier referral to early intervention during critical periods of child development

### **Author Contributions:**

All authors have participated in the concept and design of the paper and in drafting and revising the manuscript.

SM retrieved and analysed register data

KW wrote the developmental section

CM searched, critiqued and drafted the tools section

IN drafted clinical practice algorithms

NOTE: Permissions to reproduce this publication for this thesis has been granted from the journal (See Appendices).

# CEREBRAL PALSY—DON'T DELAY

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Cerebral palsy (CP) is the most severe physical disability within the spectrum of developmental delay. CP is an umbrella term describing a group of motor disorders, accompanied by many associated impairments. The disability is a result of injuries to the developing brain occurring any time from the first trimester of pregnancy through to early childhood. However, for the great majority, their full etiological causal pathway remains unclear. It is important to discriminate as early as possible between: (a) mild or nonspecific motor delay, (b) developmental coordination disorder, (c) syndromes, (d) metabolic and progressive conditions, and (e) CP with its various motor types and distributions. The most promising predictive tool for CP is the general movements assessment, which assesses the quality of spontaneous movements of infants in the first 4 months of life. We propose a change in diagnostic practice. We recommend a shift away from referral for intervention following a formal (most often late) description of CP, to one of referral for intervention which occurs immediately once an infant is considered "at risk" of CP.

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Dev Disabil Res Rev 2011;17:114–129.

**Key words:** cerebral palsy; early diagnosis; general movements; perinatal risk factors; neonatal risk factors; brain injury

## INTRODUCTION

Global developmental delay is an umbrella term that describes two or more delays in the area of speech and language, social and emotional, cognitive and motor development. Children with cerebral palsy (CP) often fall under the umbrella of global developmental delay, but CP cannot be considered "delay," as children do not "grow out of it." Health professionals need to understand what clinical features distinguish CP from other motor disorders, so the most effective interventions can be commenced earlier. The American Academy of Pediatrics have developed a policy for the surveillance and screening of developmental disorders (Council on Children with disabilities et al., 2006), however this paper focusses specifically on CP. The objectives of this review are fivefold:

1. Describe the nature of CP and what makes it different to other motor or learning disorders.
2. Outline the prevalence of CP.
3. Determine who is at high risk of CP, what are the predictors and early signs?
4. Identify tools that help clinicians to accurately predict CP.

5. Present an evidence based algorithmic approach to recognizing CP and developing intervention plans.

In the early months of life, global developmental delay and CP present similarly, if delayed, acquisition of developmental milestones is the only comparator. It is the movement disorders (e.g., spasticity and dystonia), the level of functional impairment, and the associated impairments that set CP apart from other milder motor disorders or learning disorders such as developmental coordination disorder (DCD). DCD is less severe and 25 times more common than CP affecting ~5–6% the population and current practice is not to diagnose before the age of 5. As a result, the diagnosis of CP is often delayed while the possibility of DCD is explored.

DCD is primarily a learning problem where children can achieve normal movement patterns and skills but have problems with learning and planning the movements. CP conversely is a physical disorder, where children are not able to achieve the normal movement patterns and the primary problem is motoric not learning, although deficits in learning may compound the motor problem.

DCD is used to refer to children who fulfill a certain criteria; poor motor performance which significantly interferes with activities of daily living which are not explained by any medical, neurological, or psychosocial condition. Thus a child with CP whose motor disability is neurological cannot have a diagnosis of DCD [Blank et al., 2011]. The physical disability of CP is life-long whilst DCD is more apparent in the window where the child is learning key motor skills for example, catching a ball, dressing independently, and handwriting.

## WHAT IS CEREBRAL PALSY?

CP is an umbrella term which "describes a group of disorders of the development of movement and posture, causing activity limitations, which are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain.

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Received 3 September 2012; accepted 5 October 2012

View this article online in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/ddrr.1106

**Table 1. Classification by Motor Type**

		ACPR <sup>a</sup> + Reid, 2011a
Spasticity:	Overactive muscles that display a velocity-dependent resistance to stretch. Spasticity can cause secondary impairments such as loss of muscle length, joint dislocation and pain.	85 – 91%
Dyskinesia:	Dyskinesia is either athetosis or dystonia. Athetoid CP is hypotonic with hyperkinesia characterized by involuntary writhing-stormy movement and can co-occur with chorea. In contrast, dystonic CP is hypokinetic, involving involuntary, abnormal twisting postures or repetitive movements with hypertonia. Tone is typically fluctuating.	4 – 7%
Ataxia:	Ataxia results in tremors with a shaky quality. Ataxic CP involves a loss of muscular coordination where movements have abnormal force, rhythm, and accuracy.	4 – 6%
Hypotonia:	Pure, generalized hypotonia (decreased muscle tone) is the least common CP motor-type. Some argue that pure hypotonia should not even be considered a cerebral palsy sub-type.	2%

<sup>a</sup>Australian Cerebral Palsy Register.

The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder” [Bax et al., 2005]. This most recent definition acknowledges the complexity of the condition and the impact of the associated impairments.

### What are the Fundamental Facts We Know About Cerebral Palsy?

#### *Classification of cerebral palsy guides intervention decision making*

CP is a heterogeneous condition, and to elucidate prognosis and guide selection of the most appropriate interventions (e.g., constraint induced movement therapy for hemiplegia and selective dorsal rhizotomy for diplegia) three major classifications are applied; motor-type, topography, and function. Clinicians often remark that a child may have two or three different descriptions of their CP within one medical file, evidencing the poor reliability of these traditional classification systems. Tables 1 and 2 outline the traditional motor types and topographies of CP and the proportions of a CP population with each type. In this paper, we refer to the Australian Cerebral Palsy Register (ACPR) when reporting rates and for international comparisons the Swedish Register and a study by Reid et al. [2011a] where registers throughout the world are compared.

To solve the problem of low inter-rater (and sometimes intra-rater) reliability

when identifying topographical subtype, the Surveillance of Cerebral Palsy Europe [SCPE, 2000] has recommended that traditional topographies be combined into two easily definable topographies: Unilateral (one side of the body), Bilateral (both sides of the body). The ACPR instead applies a limb by limb coding using the Australian Spasticity Assessment Scale (ASAS) [Love, 2007]. The ASAS scores the muscles’ response to rapid passive movement without the subjectivity and wording ambiguities of the modified Tardieu and Ashworth scales [Mutlu et al., 2008]. Nonspastic motor types are also coded, resulting in a “stick figure diagram” of motor impairment, which provides an objective picture of the CP. Figure 1 presents the CP description form. The descriptive form is also clinically useful for treatment decision-making, such as pharmacological options

and contracture management. The ASAS is currently undergoing further reliability studies, but it is freely available for use along with the description of CP form: [http://www.kemh.health.wa.gov.au/services/register\\_developmental\\_anomalies/documents/CP%20Description%20Form%20-%20WARDA%20website.pdf](http://www.kemh.health.wa.gov.au/services/register_developmental_anomalies/documents/CP%20Description%20Form%20-%20WARDA%20website.pdf).

The gold standard tool for reliably describing motor function in CP is the gross motor function classification system (GMFCS) [Palisano et al., 1997]. GMFCS provides a common language that conjures up a “picture” of a child with CP. GMFCS is a five level classification system of gross motor function in people with CP. The classification is based on the person’s ability to self initiate movement with a focus on sitting, transferring, and mobilizing [Palisano et al., 1997]. Different classification descriptions exist at different age groups. Table 3 summarizes the system for 2–4-year olds, to coincide with the most common time of recognition and the proportion in a CP population with each level of GMFCS.

It should be noted that whilst the GMFCS classification can be applied to infants, about 40% change classification levels by age 2. After 2 years, the classification system is stable and thus GMFCS reassessment is recommended after age 2 [Gorter et al., 2008]. This is clinically and diagnostically very important, because parents are anxious to learn early about the severity of their child’s condition for future planning but in reality the most accurate description of function and severity can only be given at 2 years.

*The presence of associated impairments and functional limitations affects the child’s outcome*

For many children with CP, it is not just a physical disability. When seeking to prognosticate the severity of

**Table 2. Classification by Topography**

		ACPR <sup>a</sup>
Hemiplegia:	Hemiplegia/monoplegia is the involvement of one side of the body. The upper limb is usually more affected than the lower limb. Strong early hand preference or hand disregard is sometimes the first sign of a problem.	38%
Diplegia:	Diplegia is where both the legs are affected and are more affected than the upper limbs.	36%
Quadriplegia (Tetraplegia)	Quadriplegia refers to the presence of spasticity in all four limbs; where the affect on the arms is equal or more than the legs. Trunk and oro-facial involvement is also to be expected. In rare cases, one limb is spared and this is referred to as triplegia.	26%

<sup>a</sup>Australian Cerebral Palsy Register.

**Table 3. Classification by Gross Motor Function at 2–4 Years**

		ACPR <sup>a</sup>
Level I:	Floor sits independently, hands-free. Walks without assistive devices.	32%
Level II:	Floor sits independently, hands-free with balance affected. Walks using an assistive mobility device.	27%
Level III:	Floor sits using w-sitting. Walks short distances indoors using a hand-held mobility device with assistance.	12%
Level IV:	Floor sits when placed, uses hands for balance. Rolls, creeps or crawls for short distances.	14%
Level V:	Unable to sit independently. No form of independent mobility.	15%

<sup>a</sup>Proportion in Australia with each level of GMFCS.

CP and determine intervention plans, assessment of associated impairments must also occur. The likelihood and severity of associated impairments increase with the severity of motor impairment [Himmelman et al., 2006; Odling et al., 2006]. Some have reported that associated impairments impact more on function and quality of life than the motor impairment [Himmelman and Uvebrant, 2011]. A meta-analysis of CP registers calculated the overall rates of associated impairments and functional limitations in the CP population to be: three in four are in pain; one in two have an intellectual disability; one in three cannot walk; one in three have a hip displacement; one in four cannot talk; one in four have epilepsy; one in four have a behavior disorder; one in four have bladder control problems; one in five have a sleep disorder; one in five dribble; 1 in 10 are blind; 1 in 15 are tube fed; and 1 in 25 are deaf [Novak et al., in press]. Many will have a number of these impairments, and the presence of these impairments complicates therapy, decreases health status and quality of life for the individual and their family, and increases costs for the family and to society. The associated impairments of CP will now be discussed briefly.

**Epilepsy.** Epilepsy can potentially severely limit the quality of life for the person with CP and their family, and adults with CP and epilepsy are less likely to find employment [Michelsen et al., 2005]. Epilepsy occurs in 30% of individuals with CP [Arnaud et al., 2008; ACPR Group, 2009]. In 2% of individuals with CP, their epilepsy will be resolved by the time they turn 5 years of age [ACPR Group, 2009]. For those whose seizures are not resolved, epilepsy is a lifelong condition. Rates of epilepsy are higher in those with: spasticity born

at term (48%) compared with preterm (28%); bilateral CP (34–87%) compared with unilateral (23%); and those with intellectual impairment (61%) compared with no intellectual impairment (19%) [Carlsson et al., 2003; Wichers et al., 2005; Himmelman et al., 2006].

**Intellectual impairment.** Intellectual impairment can be defined by low general intellectual functioning as measured by IQ scores, in combination with difficulties with adaptive behavior, all manifesting before the age of 18. Practically, this means that people with an intellectual impairment have memory deficits, difficulty reasoning, learning new skills, attending and organizing information. 50% of individuals with CP have an intellectual impairment and between 20 and 30% [Jarvis et al., 2005; McManus et al., 2006] have a severe intellectual impairment. Formal assessment of intellect is essential (but at times difficult) for an individual with CP.

**Communication.** Communication disability can have a major impact on the individual with CP and their family. Impairment in this domain can impact on both understanding of language and expression. For individuals who have severe communication impairment, social isolation and poor self-esteem can result. Between 20 and 30% of people with CP are nonverbal which means that systems to support other forms of communication are required [Arnaud et al., 2008; ACPR Group, 2009; Andersen et al., 2010; Parkes et al., 2010]. They are more likely to be nonverbal if they are non-ambulatory (GMFCS IV–V, 57%) compared to those who are able to walk (GMFCS I–III, 4%) [Shevell et al., 2009]. Augmentative and alternative communication (AAC) systems, which can range from low/light technology systems such as signing or use of alphabet charts to high

technology systems such as speech generating devices, may be used to communicate. It is a fundamental human right to have the opportunity to communicate; however, high technology AAC systems are expensive, requiring wait listing and for some individuals will mean that they are unable to access systems that would support them to communicate.

**Vision.** Vision impairments can range from mild requiring glasses, to functionally blind. About 5–12% of individuals with CP have a severe impairment, or are functionally blind [McManus et al., 2006; ACPR Group, 2009]. Another 30% will have a mild to moderate vision impairment.

**Hearing.** Hearing impairments can also range from a mild impairment to bilateral deafness. Bilateral deafness occurs in 2% of people with CP while other hearing impairments occur in a further 10% [Surman et al., 2006; ACPR Group, 2009]. Assessment of vision and hearing in children with CP should be thorough and done early, as it can impact greatly on their ability to learn and achieve milestones.

**Other.** Other impairments strongly associated with CP are hip dislocation (8%), displacement (27–35%) [Hagglund et al., 2005; Soo et al., 2006] and spine deformities, sleep disorders (23%) [Newman et al., 2006], pain (70%) [Jahnsen et al., 2004; Arnaud et al., 2008], eating (8% tube fed) [Shevell et al., 2009; Sigurdardottir and Vik, 2011], excessive drooling (22%) [Parkes et al., 2010], bladder and bowel control complaints (24%) [Roijsen et al., 2001], and behavior difficulties (26%) [Parkes et al., 2008]. These less well-understood impairments are more likely to occur with bilateral CP and intellectual impairment.

*CP is the most common physical disability in childhood with prevalence unchanged for 60 years*

The overall prevalence of CP is ~0.2% of the population (i.e., 1 in 500) in developed countries. As can be seen by a projected age distribution of one state in Australia (Fig. 2), even though the injury responsible for CP occurs in the developing brain, it is a lifelong condition, with most patients having a normal life expectancy. In reality, CP is not just a condition of childhood.

The true incidence of CP cannot be estimated as there are a proportion of infants who die in the intrapartum, neonatal and infant period, who had brain lesions that may or may not have met



**DESCRIPTION OF CEREBRAL PALSY Part I: MOTOR IMPAIRMENTS**

Child's name: \_\_\_\_\_ DOB: \_\_\_\_\_ Examining clinician: \_\_\_\_\_ Date: \_\_\_\_\_

**1. Is there spastic tone in one or more limbs?**

Yes ☐ No ☐

Please tick Yes / No boxes as appropriate

**2. Is muscle tone varying?**

Yes ☐ No ☐

**3. Are there signs of ataxia?**

Yes ☐ No ☐

**Stick Figure 1**

**Instructions for completing Stick figure 1 above:**

<b>Axial tone</b>	Hypotonic = ↓	<b>Limb tone:</b>	Highest Australian Spasticity Assessment score in that limb (see scoring criteria overleaf)
<b>Neck tone</b>	Hypertonic = ↑		
<b>Face tone</b>	Fluctuating = ↕		
	Normal = N		

**Go to 2**

**Stick Figure 2a**

**Stick Figure 2b**

**Instructions for completing Stick figures 2a and 2b above:**

Please tick boxes and/or circles where signs are present.

**Go to 3**

**Is there generalised hypotonia with increased reflexes?**

Yes ☐ No ☐

**Please number tone/movement abnormalities present in this child in order of predominance (1 = most predominant or only abnormality)**

- ☐ Spasticity
- ☐ Dystonia
- ☐ Athetosis
- ☐ Ataxia
- ☐ Generalised Hypotonia

**Please describe CP type and severity in words as you would write in the medical record:**

\_\_\_\_\_

Form designed for the Australian Cerebral Palsy Register - 7 June 2006

Figure 1 Cerebral palsy description form. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

the criteria for CP. It has been suggested therefore that the closest rate to incidence (for CP) is prevalence of neonatal survivors (NNS). Western Australia (WA) is one register that reports in this manner, and is also one of the longest running CP Registers in the world. CP is mandatorily reported in WA, therefore it is assumed that this register has as close to a total population cohort as is possible. WA's CP rates reported in 2006 are 2.78/1,000 NNS increasing to 3.9/1,000 when post-neonatal CP is taken into account [Blair and Watson, 2006; Watson et al., 2006]. NNS are important when rates are reported by gestational age stratum. The lower the gestational age stratum, the more rates differ between NNS and live births. It is particularly important for those at the youngest gestational ages. When reporting rates in the birth years 2005 and 2006 for those born between 20 and 27 weeks in WA, the rate per 1,000 NNS was 72 (95% CI 32–110) compared to

live births 51 (95% CI 24–79) [Watson, 2012, personal communication]. If neonatal deaths are not taken into account, live births give a misleading lower rate. In term births (37+ weeks), where the rate of intrapartum/neonatal death is proportionally much less, the difference between NNS 1.7 (95% CI 1.4–2.1) and live births 1.7 (95% CI 1.4–2.0) becomes inconsequential. Despite this denominator being the most accurate, for comparison live births are the most widely used denominator.

Estimates of prevalence throughout the world vary depending on the methodology of "count," percentage ascertained and variations in selection criteria. CP Registers have identified rates ranging between 1.4 and 2.77/1,000 live births; surveillance programs range between 2.1 and 3.6/1,000 live births; and cross-sectional surveys range between 1.05 and 4.1/1,000 live births. The two largest data sets, the ACPR and the SCPE both have an overall

birth prevalence of 2/1,000 live births. In developing countries, it is thought that incidence is higher as the public health measures that help prevent some CP cases are not freely available in developing countries [Blair and Watson, 2006]. All data sets across the world agree there is a higher proportion of boys diagnosed with CP. Although CP is found across all socio-economic classes, there is a clear association between low birth weight and low socio-economic status, and in normal birth weight ranges, rates of CP are 2.42/1,000 live births for those in the lowest socio-economic groups, compared to 1.29/1,000 for the most affluent groups.

The overall rate of 2/1,000 has been fairly stable over the last 60 years in contrast to the dramatic falls in perinatal mortality rates. However, there have been some trends in gestational age stratum, shown in Figure 3. Rates in the extremely and very low

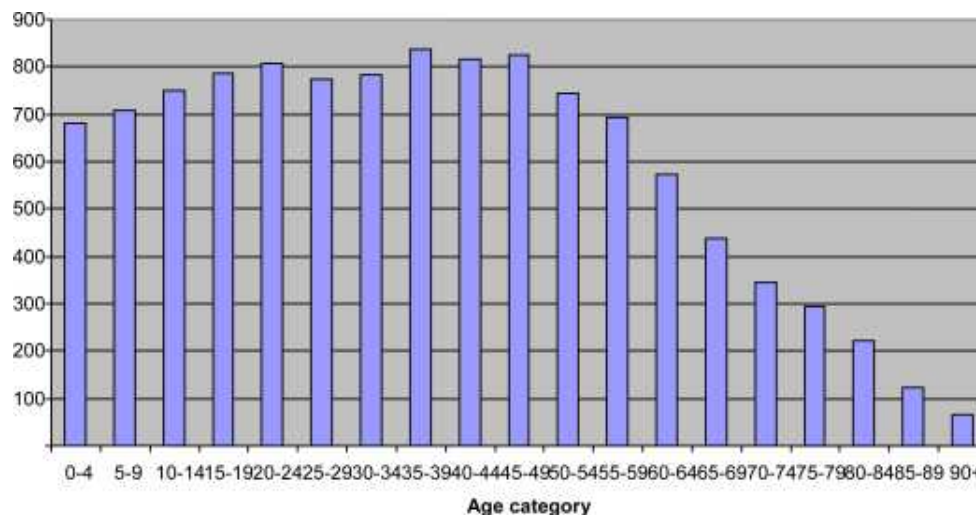


Figure 2 Estimated number of people living with CP in New South Wales, Australia. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

gestational groups rose during the 1980s, but are now trending down. Moderately premature infants' rates have decreased slightly, while in term infants the rates are unchanged [Blair et al., 2001; Watson et al., 2006]. Because the majority (>73%) of infants are born over 32 weeks gestational age, the increases and decreases in the extremely and very preterm groups have made little difference to the overall rate.

*Identification of infants "at-risk of cerebral palsy" is possible; assessment and screening should follow*

Since there are no identifiable biomarkers to accurately predict CP, and clinical risk factors only identify subpopulations of infants at risk [McAdams and Juul, 2011], understanding the term "causal pathways" is important. CP etiologies are described in terms of causal pathways, as there is very rarely one specific cause of brain damage severe enough to cause CP. Much research has been published that attempts to discern the risk factors that lie on one or more causal pathways to CP. What researchers are beginning to realize is how little is known about how these risk factors interact on causal pathways. Risk factors can be described according to when they occur or when they are identified. The following examples have been identified for CP:

- Prior to conception: Previous gynecological history of stillbirths/multiple miscarriages/neonatal death/premature birth, family history of CP and other genetic predispositions, maternal diagnoses, for

example, intellectual impairment, epilepsy and low socioeconomic status.

- Early pregnancy: Infection, birth defects, multiple births, male gender, and other genetic predispositions.
- During pregnancy: Maternal disease, for example, thyroid disorders, pregnancy complications, for example, preeclampsia and bleeds in the second and third trimester, infection and inflammation, intrauterine growth restriction (IUGR), placental abnormalities and other precursors to premature birth.
- Around the time of birth and the neonatal period: An acute intrapartum hypoxic event, stroke, seizures, hypoglycemia, jaundice, and infection.
- Postnatal period: Infections, accidental and nonaccidental injuries, stroke both spontaneous and following surgery.

The rate of CP in neonatal survivors varies significantly with level of risk at birth. To describe the risk of developing CP, infants have been separated into three distinct groups shown in Figure 4: (1) premature infants (30–40% of all CP); (2) term born infants who shortly after birth have neonatal encephalopathy (NE), a clinically defined syndrome of disordered neonatal brain function (15–20% of all CP); and (3) term born "healthy" infants, who do not require special care in the neonatal period (40–50% of all CP) and do not appear to have identifiable risk factors at birth [Badawi et al., 2005; Wu et al., 2006; McIntyre et al., 2011]. *Premature infants.* When considering which babies are at risk of CP, preterm infants commonly come to mind. The risk of CP increases as gestational age

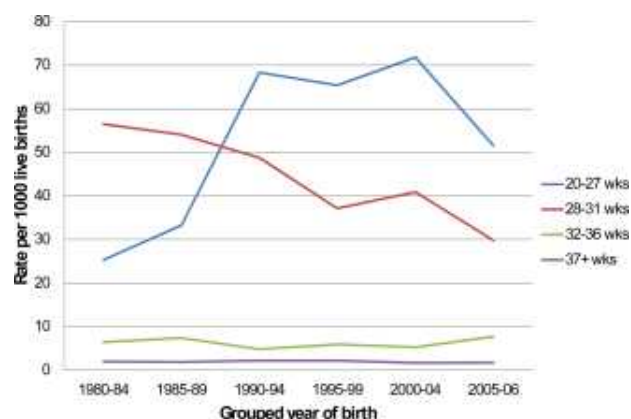


Figure 3 Gestational age specific rates/1,000 live births in WA, 1980–2006. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

decreases, therefore babies born at 36 weeks' gestation are at much lower risk than those born at 24 weeks. As a result, rates in premature infants range between 3 and 80/1,000 neonatal survivors, reflecting the wide variation in levels of risk across premature gestations. Premature infants constitute up to 40% of infants who develop CP [Kirby et al., 2011]. So why are premature infants at increased risk of CP, and which ones are at the highest risk?

The group of preterm infants can be separated according to gestational age, with the first subgroup being extreme prematurity, generally considered less than 28 weeks' gestation. There is much data in the literature which depicts the outcomes of extremely premature infants and much research has been conducted in this age group [Hoon and Faria, 2010; Reid et al., 2011b]. In the 1970s and 1980s, the frequency of CP in this gestational age group increased. This was attributed to the increasing survival of extremely preterm infants and their predilection to germinal matrix hemorrhage and periventricular leukomalacia (PVL) [Stanley and Watson, 1992; Hagberg et al., 1996]. Evidence from population-based samples in Europe, Australia and the United States, and analyses from CP Registers in Australia and Europe describing trends in prevalence, subtypes, and severity, suggest that this rise in frequency of CP in extremely preterm infants has reached its peak and is now decreasing [SCPE, 2000; Reid et al., 2011b; Watson, 2012, personal communication]. Up to 10% of extremely preterm infants (variations in reports exist from as low as 3–10%) and up to 5% of infants between 28 and 31 weeks gestation will be described as having CP [Himpens et al., 2008; Watson, 2012, personal communication].

**Practice point.** Mothers whose labor is imminent (and prior to 30 weeks gestation) should now be offered magnesium sulphate for neuroprotection of their child. Meta analyses have shown that CP can be reduced by 30% for infants under 30 weeks gestation [Crowther et al., 2002].

CP Registers in Europe report that this trend for decreasing rates continues into the group of late preterm infants (32–36 weeks' gestation or 1,500–2,499 g) [Andersen et al., 2011]. The overall prevalence of CP in these children had dropped from 12.2 per 1,000 live births in 1983 to 4.5 per 1,000 in 1997. There is conflicting evidence in Australia, with the rate being

maintained at between 5 and 7/1,000 live births since the early 1980s [Watson et al., 2006].

Cerebral lesions in particular PVL, intraventricular hemorrhage (IVH) and intracranial hemorrhage (ICH) grade III and IV, are the most important predictors of CP in very preterm infants [Tran et al., 2005; Beaino et al., 2010; Himpens et al., 2010]. In particular, PVL lesions in the corona radiata above the posterior limb of the internal capsule (PLIC) observed in coronal sections have been used to accurately predict motor prognosis [Nanba et al., 2007]. The presence of lesions in this region was highly predictive of CP (GMFCS 1 or higher) with sensitivity 100% and specificity 97%. A study by Himpens et al. [2010] that investigated the predictive value of ultrasound in brain injury found that deep grey matter lesions are a significant predictor for severe versus mild and moderate CP (OR = 6), and that cerebral infarction and hemorrhage grade IV are strong predictors of unilateral spastic CP versus bilateral spastic CP (OR = 49 and 24, respectively,  $P < 0.001$ ).

Recently, there has been increasing interest in and evidence regarding the possible effects of intrauterine infection or inflammation early in the postnatal course, leading to CP. Carlo et al. [2011] recently argued that a late prenatal and/or early neonatal exposure to inflammation may predispose infants to neurodevelopmental impairment. Wu and Colford [2000] also found that clinical chorioamnionitis was associated with an increase in CP in preterm infants (OR = 1.9) and term infants (OR = 4.7).

Transient hypothyroxinaemia, bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis have also been associated with premature birth and a later description of CP. A recent study of 1,047 preterm infants (<28 weeks) demonstrated that while all infants with BPD had a higher risk of CP those who were mechanically ventilated until 36 weeks PMA had at least a fourfold increased risk of CP [Van Marter et al., 2011]. In addition, preterm infants who have had surgery to repair a patent ductus arteriosus, or who required home oxygen have also been identified as at increased risk of CP [Tran et al., 2005].

**Practice point.** Infants born premature are at high risk of CP if they have abnormal cerebral imaging and a more complex course. These infants should

receive a general movements (GM) assessment before term equivalent age, and be referred to active surveillance and early intervention when they leave the hospital. (see Pathway A Figure 5, to be discussed in the following section).

#### *Term infants with and without neonatal encephalopathy*

The overall rate of CP for term infants has been consistently 1.4–1.7/1,000 live births over the past 30 years [Watson et al., 2006; Himmelmann et al., 2010]. Multiple births born at term are at four times the risk of CP than singletons born at term. The risk rises again for surviving twins after the death of a cotwin [Pharoah, 2006]. Risk factors associated with the development of CP in the term population also include congenital malformations, maternal age over 35 years, chorioamnionitis, preeclampsia, placental abnormalities, meconium aspiration syndrome, IUGR, transient metabolic abnormalities, respiratory distress syndrome, neonatal infections and seizures. [Shankaran, 2008; McIntyre et al., 2012]. One of the most well known risk factors for term-born infants is NE.

The second piece of the pie (Fig. 4), with a well-recognized predilection to develop CP are term or near term infants with NE. For term born infants with NE, the rate of CP is between 100 and 125/1,000 neonatal survivors, and those born with severe NE are at the highest risk of CP of all infants. Infants with moderate to severe (Sarnat Stage 2 or 3) NE account for one in four cases of term CP [Badawi et al., 2005]. Kurinczuk et al. [2010] report an incidence of NE between 2.5 and 3.5 per 1,000 live births and that ~30% of cases in developed countries are associated with evidence of an acute intrapartum hypoxic event. These include sentinel birth events that are also rare but important risk factors for CP in term infants, such as placental abruption, cord prolapse, severe intrapartum hemorrhage, severe shoulder dystocia, and a tight nuchal cord. It is estimated that up to 8% of CP is attributable to an acute intrapartum event with moderate to severe NE [Blair and Stanley, 1997].

**Practice point.** Infants with moderate to severe NE following an acute intrapartum event benefit from hypothermia. This intervention prevents CP in one out of eight of those treated [Jacobs and Tarnow-Mordi, 2010]. A number of



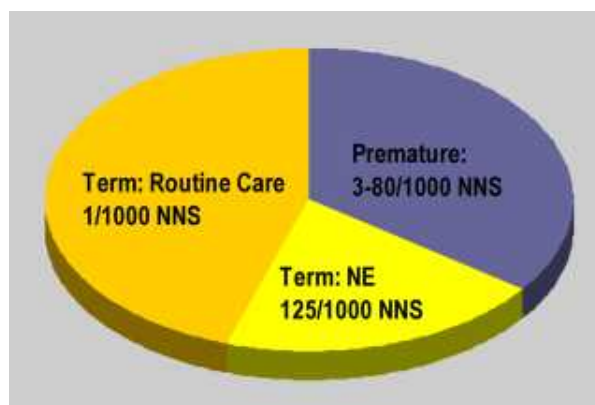


Figure 4 Rate of CP in NeoNatal Survivors. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

adjuvant therapies to help those that do not respond to cooling alone are currently in animal model and phase 1 neonatal studies, for example, erythropoietin, melatonin, xenon, and topiramate [Gonzalez and Ferriero, 2009].

In term infants with moderate to severe NE, imaging showing basal ganglia/thalamus injury has a positive predictive value for CP of 88% [de Vries et al., 2011]. In a study of 173 term infants with NE, the basal ganglia/thalamus pattern of injury was associated with the most severe motor and cognitive outcomes at 30 months [Miller et al., 2005].

**Practice point.** Term infants with moderate to severe NE and a basal ganglia/thalamus injury should be automatically described as “At high risk,” and go straight to Pathway B (Figure 5). They should receive a GMs Assessment, be referred to active surveillance and early intervention when they leave the hospital.

The remaining infants with NE that go on to be described as having CP have antenatal risks such as IUGR, intrauterine infection, metabolic abnormalities, syndromes, and birth defects [Badawi et al., 1998; Kurinczuk et al., 2010]. Perinatal arterial stroke occurs in ~1.7/100,000 live births. In the newborn period, it can also result in NE, but the majority of these infants present after the immediate neonatal period with seizures or hemiparesis. Mothers with preeclampsia and infants who have IUGR are at risk of perinatal arterial stroke [Shankaran, 2008]. Stroke with abnormalities involving the cerebral peduncle are also highly predictive of CP PPV 78% [de Vries et al., 2011].

**Practice point.** Infants with a cerebral birth defect, or stroke with involvement

of the cerebral peduncle should be identified as “at risk” of CP and should join Pathway B (Figure 5) at “assessment for CP.”

The risk of developing CP in term infants who have received routine care at birth, the third group of infants who go on to develop CP, is ~1/1,000 neonatal survivors and these infants are at the lowest risk. However, they represent 45% of all infants with CP and numerically comprise the largest group (Fig. 4). Why do these apparently “neurologically normal” children at birth develop CP, and can we identify them earlier so they can have access to active surveillance and early intervention?

From a total population case control study in Western Australia, McIntyre et al. [2011] compared the clinical descriptions of 295 term infants with CP with 442 term control infants none of which required special care. They identified six independent predictors of CP in the neonatal period: abnormal fontanelle OR 4.4 (95% CI 0.8–23); abnormal tone OR 7.3 (95% CI 2–26.8); birth defects identifiable in the newborn period OR 5.2 (95% CI 2.4–10); ventilatory assistance restricted to the labor room only OR 2.9 (95% CI 2.2–12); abnormal consciousness referred to irritability and lethargy, but none were comatose OR 3.7 (95% CI 2–7); and in the small group with abnormal temperature regulation temperature was down or fluctuating, not high OR 4.1 (95% CI 1.2–14). A number of these predictors are reminiscent of criteria for mild NE, and the presence of two or more of these factors yielded a high specificity (99%), but low sensitivity (14%) for CP. This is not surprising considering the unknown etiology of this group of infants. Of this low risk group who had CP, 58% did

not have any of these neonatal factors, yet 60% of these infants had moderate to severe CP.

This is not the first time a finding like this has been reported. The National Collaborative Perinatal Project reported that most children with CP did not derive from groups at high risk (low Apgar scores, or the presence of neonatal signs). About 43% were examined and classified as “neurologically normal” in the neonatal period and concluded that a large proportion of CP cases remain unexplained [Nelson and Ellenberg, 1986; Ellenberg and Nelson, 1988]. Earlier still, in 1970, Eva Alberman attempted to model what were at that time the three most important risks around birth: (1) parity >4; (2) abnormal method of delivery—breech, face or shoulder delivery, internal version, or delivery by an untrained person; and (3) neonatal illness in the 1st week of life—convulsions, cyanotic attacks, cerebral signs, hypothermia, jaundice, Rh incompatibility, or serious illness. Infants were at the highest risk of disability when all three of these risks were apparent. They were only a small group (0.1% of total births), but more importantly only 0.2% of those with a disability. When any combination of these three risks were used, 13.2% of all live births were classified as at risk, and this identified 26.3% of all those with a disability. A striking finding was that 74% of all those with CP, severe mental handicap, hearing, and sight impairments could not be identified using this model.

Very little has changed for those born at term without any noticeable signs during the neonatal period since the first studies of these cohorts in the 1950s. For these infants, failure to reach major motor milestones, such as rolling, sitting or standing, have often been the catalyst for the commencement of developmental assessments and interventions. Given that the window for milestone attainment in typically developing children is quite broad [WHO Multicenter Growth Reference Study Group, 2006], this usually leads to a “wait and see” approach where infants receive no intervention during their period of rapid neural development. In view of the fact that every second child with CP will be born at term and requires no special care in the neonatal period, it is imperative that frontline health professionals such as pediatricians, general practitioners and allied health practitioners have a best practice pathway to follow when a parent

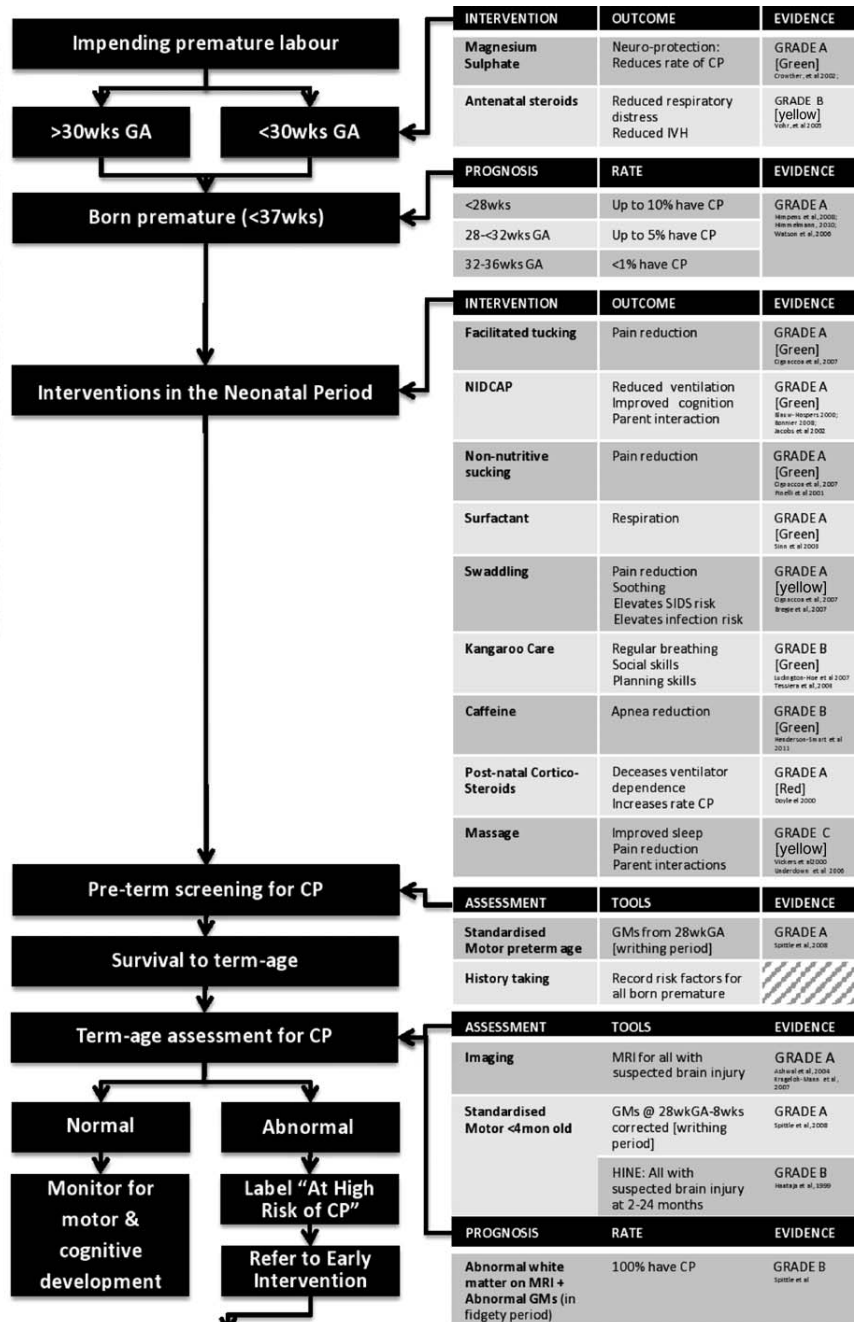


Figure 5 Recommended assessment for identification of infants at risk of CP.

presents with a child who falls into this category.

**Practice point.** When parents bring their term born child (3 months to 3 years of age) that did not require special care when born to a health professional with concerns regarding motor development or abnormal posturing they should go straight to Pathway B at "screen for CP." We propose that a tiered approach as developed by Rosenbaum et al. [2009] should be adopted. They recommend using the ages and stages questionnaire + three extra ques-

tions for parents. Consideration should also be given to risk factors during pregnancy and signs of mild NE in the neonatal period. When an abnormal result is derived, Pathway B (Figure 5) should be followed to "assessment for CP" through standardized motor assessments.

*The description of cerebral palsy is traditionally given late but can be given earlier*

This review is timely as "it is now universally accepted that the earliest possible diagnosis and treatment (of

CP) are essential to prevent, or at least minimize, the handicapping effects of a disability and to make the most of the assets a child possesses" [Alberman and Goldstein, 1970]. Yet, paradoxically, 40 years later families are not automatically receiving early intervention while they "wait and see" whether their child will "catch up" from simply a slower motor developmental trajectory or if their child actually has CP or DCD or an intellectual impairment with associated motor difficulties.

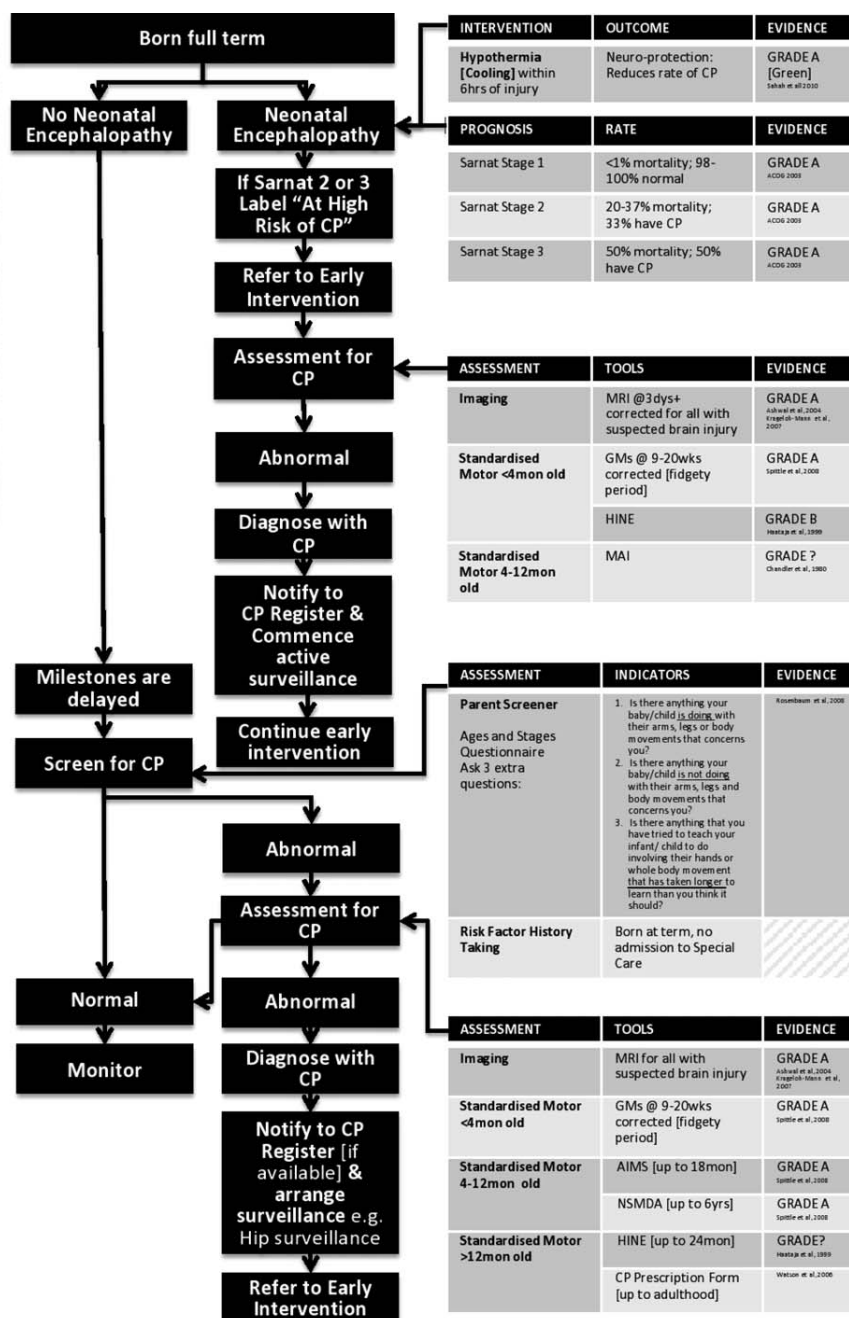


Figure 5 (Continued)

CP registers indicate the average age for a description of CP to be given is 19 months, but the range is wide. For those with severe motor impairment the description of CP can be given as early as 1 week but may take up to 3 years, and less surprisingly for those with mild or moderate motor impairment the description of CP is given anywhere between 1 week and 5 years of age [Watson et al., 2006]. The burgeoning body of recent neuroplasticity literature suggests that intensive, repetitive, task-specific intervention for CP ought to commence very early

while the brain is most plastic (i.e., in the first 2 years of life), which is almost never the case when the family is taking part in "wait and see" monitoring prior to description.

Good evidence shows that earlier detection of CP is both possible and accurate and, more importantly, diagnostic-specific early intervention is therefore possible. Rather than waiting for a formal description of CP to be given, infants should be identified as "at high risk of CP" when they are high risk, and therefore commence diagnostic-specific early intervention straight

away. For those who are not at high risk but have early signs, they should be regularly comprehensively assessed to ensure access to the most appropriate early intervention.

### Why is Cerebral Palsy Missed and Why is the Description so Difficult for Doctors to Make?

Health professionals hesitate to use the terminology CP early for a number of reasons, but importantly the condition is not a diagnosis; it is a "clinical description." There are no biological markers or definitive tests for CP. The

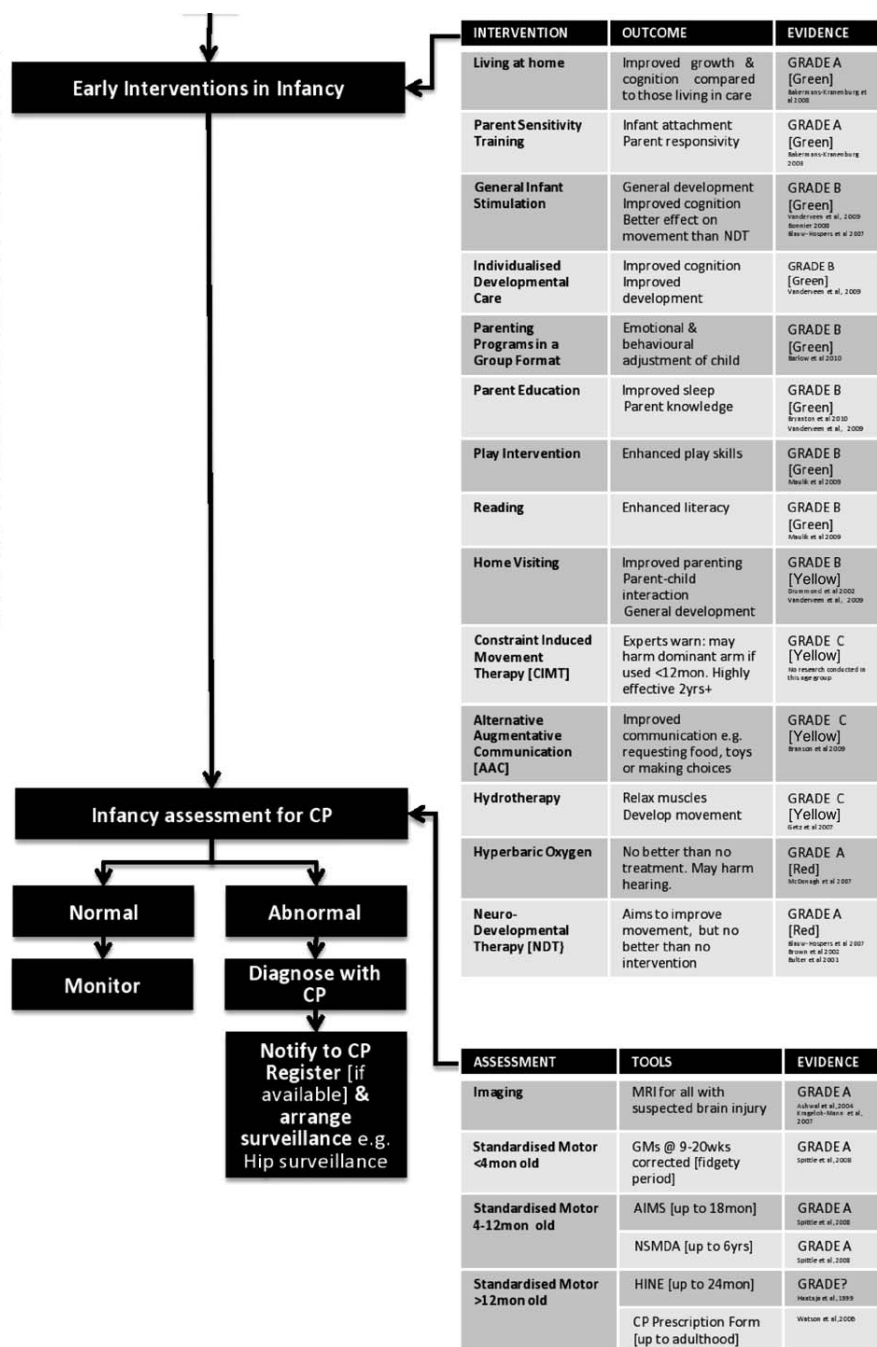


Figure 5 (Continued)

term does not infer etiology, and it has no prognostic value as severity and associated impairments are incredibly variable. However, 86% of parents know something is wrong with their child before a description of CP is given [Baird et al., 2000]. Leading up to this point in time, most parents experience being told by their medical team that the plan is to “wait and see.” When health professionals use the term “wait and see,” the intention is to use this time to rule out other diagnoses, delay the delivery of

bad news or provide time for the child to grow out of it.

#### Rule out other diagnoses

Doctors first rule out other diagnoses that may explain the symptoms. This is an important step as there are other conditions that mimic the early signs of CP which can have important treatment implications, such as: neuro-degenerative conditions (e.g., Ataxia Telangiectasia); metabolic syndromes (e.g., Glutaric acidemia); and genetic

conditions (e.g., Trisomy 18, Angelman Syndrome, Cornelia de Lange syndrome) [Badawi et al., 1998].

#### Delay the delivery of bad news

Doctors sometimes delay the delivery of bad news while exploring the possibility of a less severe, more common disorder such as DCD. Differential diagnosis is critical as it informs the selection of intervention strategies suited to the specific condition. For example, effective intervention for



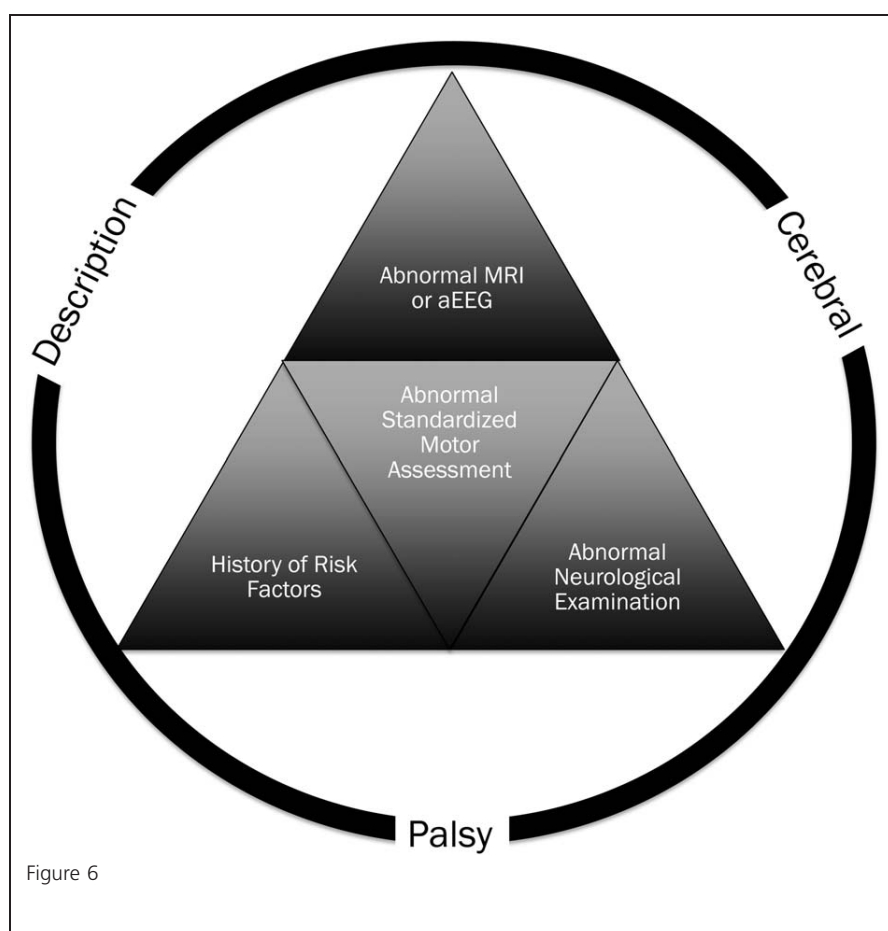


Figure 6

pediatrician who may lack access to the relevant maternal-fetal and/or neonatal medical history. The pediatrician may then be assessing a healthy baby that may just appear slightly “delayed,” and it is not until later in infancy that the gravity of the problem may be evident, precipitating a late diagnosis.

### What are the Most Important Things that can be Done in Clinical Practice to Describe Cerebral Palsy Earlier?

We propose a new clinical pathway that is designed to circumvent the existing screening and diagnostic barriers by tying together the relevant evidence needed to make an earlier diagnosis and commence earlier intervention (see Pathways A and B). These pathways have been developed using GRADE level evidence [Guyatt et al., 2008] and “traffic lights” to signify the effectiveness of the interventions [Novak and McIntyre, 2010]. Green equals “go,” (high quality evidence to support the use of the intervention, therefore use this approach). Yellow equals “measure” (low quality or conflicting evidence supporting the effectiveness of the intervention). Red equals “stop” (high quality evidence indicating ineffective interventions) [Novak and McIntyre, 2010].

The serious nature of these standard care limitations has led us to conclude that “waiting and seeing” is potentially harmful to children with CP and their families. We therefore have identified solutions to three of the major problems relating to the late diagnosis of CP, which are timely and possible for the health system to redress:

#### *New clinical diagnostic and intervention pathways*

When the system fails to recognize a child with CP very early due to using the “wait and see” monitoring mode, this decision essentially ensures that infants receive limited or no diagnostic-specific intervention within the critical window of brain development. The window of brain development, where the brain is actively sprouting and pruning in response to activity, is often missed in children with CP. In Pathways A and B, we review the evidence for early intervention possibilities in CP. The evidence tells us quite clearly that general early intervention and parent interventions, designed to enhance in-home care characterized by positive interactions, categorically improve a child’s cognition with the

DCD involves cognitive approaches best suited to school-aged children, whereas CP intervention uses a variety of pharmacological, motor, social and cognitive intervention approaches that can commence early in life. It is therefore important that children with CP are differentiated earlier in order to get the right interventions early.

#### *Provide opportunity to grow out of it*

Doctors sometimes delay the delivery of bad news to provide enough time for the possibility that the child may “grow out of it.” However for those few whose motor signs resolve, commonly they transpire to have an intellectual impairment or behavioral problems [Nelson and Ellenberg, 1981].

The brain injury responsible for CP may be suspected or even confirmed in the neonatal period, but the diagnosis for many does not occur until the motor impairments and activity limitations inherent in the definition are observable. This lag time is not useful to families or to the child.

“... I am very worried about my son, he is 5 months old, and over the last month I have noticed he seems to go

into strange positions, I especially notice it each time I pick him up. I went to the GP, who agreed and thought I should see a pediatrician. I went to the pediatrician who agreed they were unusual and said let us see how he is when he is 10 months old. That is too long to wait! So I went to another pediatrician who agreed again, it was abnormal, so now I am booked to go to a physiotherapist for further tests, and after that they will decide what to do” but I do not know what to do now...” (Personal communication, February 4, 2012, parent discussion with first author over the phone).

System barriers to description are also potentially at work. For example, for any mother and her newborn, obstetricians hold vital information about maternal-fetal health. If the baby is premature or ill, care is immediately transferred to neonatal specialists, where the primary patient is now the infant, not the mother, and some of the relevant preconception and pregnancy history about risk factors for CP may not be passed on. When the infant is well and discharged from hospital, care is likely to be transferred to a community based general practitioner or

best effect seen in children of low socio-economic status. However, more recent neuroplasticity evidence suggests that a skill-based, high-intensity practice approach to early intervention is required to impact on motor outcomes, as is the case in most adult brain injuries. These newer types of motor learning approaches, which are effective in older children with CP, require urgent study within the CP infant population. It is therefore the responsibility of the health professional who observes major risk factors or a motor delay to investigate further, diagnose “at risk of CP” early, and refer to early intervention at a minimum to optimize their cognitive function. We outline a way to do this via systematic use of risk factor history taking, neurobehavioral predictive tools, in addition to MRI (Pathways A and B).

*Promotion of a climate for new research that will improve outcomes*

Late description of CP is creating a major problem for recruitment of infants to promising early rehabilitative and potentially curative studies. Lack of diagnosis is impeding the advancement of regenerative medicine, early intervention and other well-recognized treatments for CP yet to be tested in the earlier years, for example, medical interventions for tone management, reflux, and epilepsy. When a health professional identifies an infant at high risk for CP, coupled with referral to early intervention trials, it will help to accelerate future discoveries for these children and change the landscape of the diagnosis and prognosis.

*Promotion of good family mental health and resilience for the long-term*

If late description is not helping infants or research, are we helping parents by sheltering them from bad news? A population study conducted in Britain found that parental dissatisfaction with delayed diagnosis of CP is associated with higher rates of parental depression [Baird et al., 2000]. So it would appear that sparing parents from bad news is unhelpful. Therefore early recognition and provision of early preventative mental health support for families may help parents manage the inevitable stress, which could help improve family outcomes long-term.

The concept of “at risk” is not a new one. During the 1960s in the United Kingdom, there were “at risk” registers, with the usual accompanying debate over their value and cost effec-

tiveness. It was deemed not practicable to have universal screening of all children, but it was felt essential that all children at risk be monitored. In a letter to the Lancet in 1967 defending the concept, Dr Ronald Mac Keith and colleagues wrote, “by the criterion of identifying handicaps which are in some cases undoubtedly, and in other cases probably, benefited by having treatment started without delay, developmental and neurological assessment from the age of 5 months is neither difficult nor inefficient” [Mac Keith et al., 1967]. The concept itself was deemed by most to be a sound one. The problem at this time was the “at risk” criteria used was identifying up to 60% of all live births in an area. The goal of these programs was to screen 10–20% of all births to identify the majority of the invisible handicaps that is, those that would otherwise not be identified until the 4th and 5th years of life. We recommend that the “wait and see” period is reframed to the “wait and be” period, where children are diagnosed “at risk of CP” early and are immediately referred to diagnostic-specific early intervention.

### **What Tools can be Used to Accurately Predict and Identify Early Signs of Cerebral Palsy?**

#### *Imaging*

*Practice point.* All children with a presumed or suspected brain injury should have magnetic resonance imaging (MRI).

Neuroimaging is used as an integral part of the diagnostic process [Krageloh-Mann and Horber, 2007]. MRI is the gold-standard neuroimaging technique for elucidating the pathogenesis of CP: white matter damage of immaturity (WMDI) including PVL, lesions of the deep grey matter, malformations, focal infarcts, and cortical and subcortical lesions [Bax et al., 2006]. Cranial ultrasound (CUS) is a safe and inexpensive alternative used in the neonatal intensive care unit (NICU) to detect structural changes in the newborn brain. However, MRI has higher sensitivity and specificity than CUS as a predictor of CP in very low birth weight (VLBW) infants [Mirmiran et al., 2004]. Despite strong correlations between clinical findings and MRI, 12–14% of children with CP will have normal MRIs [Bax, 2006; Krageloh-Mann and Horber, 2007] and therefore MRI should not be used in isolation for making the description of CP.

Newer techniques and technologies are being developed which are likely to advance the role of imaging in the diagnostic process and treatment selection process. Advanced neuroimaging techniques such as diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) have been utilized to more specifically identify diffuse or subtle white matter injuries [Hoon and Faria, 2010]. Magnetic resonance spectroscopy (MRS), provides measures of brain biochemistry and is proving an effective tool in understanding prognosis in NE and preterm infants [Ancora et al., 2010; Van Kooij et al., 2012]. Large deformation diffeomorphic metric mapping (LDDMM), where a 3D atlas of the brain is produced, shows great promise for illuminating the structural brain abnormalities that occur in CP with the potential for informing selection, design, and measurement of rehabilitation interventions [Faria et al., 2011].

#### *General neuromotor and developmental assessments*

Many neuromotor and developmental assessments with sound psychometric properties exist for infants and young children. For diagnostic purposes, tools with predictive properties are the most worthwhile. However, there has been a historical preference by pediatricians and neonatal follow-up teams to use discriminative tools that assess a combination of: abnormal muscle tone of the trunk and extremities; the presence of primitive reflexes; the quality and quantity of voluntary movement (e.g., milestone acquisition); and the presence of involuntary movement. The problem with this persistent practice is that these tools are only useful for discriminating between infants who are developing typically from those who are not. Determining who is typically developing and who is not is even more complicated in premature infants because they have their own developmental trajectory [Heineman and Hadders-Algra, 2008; Spittle et al., 2008a]. Routinely used neuro observations and standardized developmental tests were not designed to specifically detect the presence of CP and thus further compound the complexity of the CP diagnostic process. They may be helpful to some diagnosticians but will lack adequate specificity for most.

Ideally the aim of monitoring ought to be to differentiate why some children are not developing normally, to enable diagnostic-appropriate best-

available evidence-based intervention to be provided. This paper will now focus on the evidence for the best available tools for predicting and recognizing CP, distinct from tools better suited to suspecting global developmental delay (GDD). Clinometric reviews indicate that different tools need to be used at different ages to describe and detect CP and that a combination of tools is best practice [Heineman and Hadders-Algra, 2008; Spittle et al., 2008a].

**Practice point.** A combination of risk factor history taking, neurological examination that includes assessment of quality of movement, volitional movement and neuroimaging are required. A health professional with clinical expertise and experience in motor development should interpret and evaluate the findings generated by these assessments (Figure 6).

#### *Tools predictive of cerebral palsy*

**Qualitative assessment of general movements** [Einspieler et al., 2004]. Of all the tools available to predict CP, GMs is consistently the most predictive, with specificity and sensitivity rates higher than MRI [Burger and Louw, 2009]. The GMs assessment measures the quality of spontaneous movements with the infant lying supine. Scoring is done by trained assessors via observation of video footage and can be used from the preterm period until 20 weeks post term age (PTA). Two distinct time periods for assessment exist; the writhing period (up to 9 weeks PTA) and the fidgety period (from 9 to 20 weeks PTA). In both periods, the infant is scored with “normal” or “abnormal” GMs. Abnormal GMs are then further classified. In the writhing period, abnormal GMs known as “cramped synchronized” have been shown to be highly predictive of CP (sensitivity = 100%; specificity = 40%; PPV = 9.4%; NPV = 100% [Spittle et al., 2009]. If the abnormal GM of “cramped synchronized” is followed by the abnormal GM “absent fidgety” (in the fidgety period) this has consistently shown the highest predictive value for CP (Darsaklis and Snider, 2011).

A recent systematic review of 17 studies demonstrated the accuracy of the GMs assessment in predicting neurodevelopmental outcomes in infants up to 2 years with a sensitivity  $\geq 92\%$  and specificity  $\geq 82\%$  [Burger, 2009]. The GMs assessment has been found to be superior to ultrasound findings in predicting CP [Einspieler et al., 2004]

When correlated with MRI findings, namely white matter injury, the GMs assessment (specifically “absent fidgety”) has been shown to accurately predict CP 100% of the time in very preterm infants [Spittle et al., 2008a]. Evidence of the predictive value of GMs in full term infants with hypoxic ischemic encephalopathy (HIE) has also been demonstrated [Prechtl et al., 1993]. Importantly, the GMs assessment has good clinical utility because it is quick, inexpensive, and noninvasive. Rater training is provided by the GMs trust.

**Hammersmith infant neurological assessment** [Haataja et al., 1999]. The Hammersmith assessment is based on the Dubowitz and Dubowitz [1981] assessment of the newborn and is a simple method of examining infants between 2 and 24 months of age. There are three parts to the examination: neurologic signs, developmental milestones, and behavior. In the first section, the neurologic exam, an optimality score is obtained from the assessment of cranial nerve function, posture, quality and quantity of movement, tone, and reflexes and reactions. The second and third sections do not form part of the overall score but give important additional information regarding developmental progress. Recent studies have demonstrated the predictive value of the Hammersmith infant neurological assessment (HINE) for CP. A large study [Pizzardi et al., 2008] of 658 infants who were either preterm or term with NE were prospectively studied from birth until 12 months corrected age. ROC curve analysis was used to test the predictive power of the HINE. Global HINE scores showed high prediction of CP at all ages (ROC curve areas above 0.9), but most importantly movement quality and quantity test items had even higher predictive power.

A retrospective study of 70 infants diagnosed at 2 years with CP observed a strong ( $r = -82$ ) negative correlation between HINE scores at 3–6 months of age and levels of GMFCS [Romeo et al., 2008a]. Infants in GMFCS levels 3–5 scored below 40, whereas those in levels 1–2 scored between 40 and 60. Combined use of the HINE and GMs at 3 months PTA can be used to describe an infant as at “high risk” of CP [Romeo et al., 2008b].

**Practice point.** Routine follow-up for preterm and sick infants should be scheduled at three-months and six-months corrected, not the conventional

four-months, to enable medical teams to use the best predictive tools to help make the description of CP earlier.

**Practice point.** When examining infants, do not discount CP when spasticity or dyskinesia is not identified. A period of time lapses between the original damage to the developing brain, whether in utero or during early infancy/childhood, and the appearance of impairments. It is well known that the brain, which begins development in utero, continues to develop during childhood. Thus a child’s neural development is “age-specific,” so brain dysfunction will manifest according to the brain’s development at that age [Hadders-Algra, 2004]. Compared with a mature brain which responds to injury with specific and localized signs, a young infant may present with generalized and nonspecific signs (e.g., hypotonia) [Kuban and Leviton, 1994; Hadders-Algra, 2004]. It is proposed that further brain development in an infant, including myelination of axons and maturation of basal ganglia neurons, must occur before spasticity and dyskinesia can manifest [Kuban and Leviton, 1994]. The infant with hypotonia may thus “develop” spasticity and dyskinesia by the age of 1 or 2 years, as the complexity of neural functions increases [Kuban and Leviton, 1994; Hadders-Algra, 2004].

**Movement assessment of infants** [Chandler et al., 1980]. The movement assessment of infants (MAI) is a criterion-referenced scale that evaluates neuromotor dysfunction in high risk infants at 4, 6, 8, and 12 months of age. The assessment is carried out by a therapist and takes 30–60 min to complete, requiring a manual but no specialized equipment. The MAI assesses tone, primitive reflexes, equilibrium reactions, and volitional movement. The test has been shown to be twice as sensitive as the Bayley scales of infant development in detecting early signs of CP [Harris, 1987]. Studies of predictive values at 4 and 8 months of age report sensitivity rates ranging from 73.5 to 96.0 and specificity of 62.7–78.2 [Spittle et al., 2008b]. A recent investigation of the predictive validity of the MAI at 6 months of age demonstrated a significant correlation between MAI scores and Bayley scales of infant development at 12 months, although sensitivity and specificity for CP were not reported [Metgud et al., 2011].

**Other useful assessments.** Several other neuromotor assessments, such as the test



of infant motor performance (TIMP) [Campbell, 2005], The neuro-sensory motor development assessment (NSMDA) [Burns et al., 1989], and the Alberta infant motor scale (AIMS) [Piper and Darrah, 1994], are appropriately used to discriminate infants with abnormal motor function from those typically developing. All have sound psychometrics. Of these tools, the TIMP has been shown to be sensitive to change in response to intervention [Campbell et al., 1995].

#### Assessment summary.

- High risk infants should be routinely assessed using the GMs preferably three times; during early admission, around term corrected (if preterm) and at 9–14 weeks (corrected for gestational age).
- “High risk of CP” designation should be given to infants at 9–14 weeks (corrected) with a combination of absent fidgety GMs and white matter injury on MRI.
- After 20 weeks (corrected), use the HINE or MAI.
- MRI is the best imaging tool to elucidate the pathogenesis of CP and should be offered to all infants who have abnormal findings.
- Use the CP description form to describe motor type and severity to inform intervention planning.

## CONCLUSION

Until recently, CP was considered unpreventable, incurable, and almost untreatable. However, preventive efforts including: rubella vaccination, iodine supplementation in areas of severe iron deficiency, anti-D vaccination, preventing methyl-mercury contamination, reducing the number of embryos transferred in invitro fertilization (IVF) (in Australia), and enforcing laws for seat belts and fencing around swimming pools have been successful prevention strategies. Recently, magnesium sulfate and hypothermic intervention have also started to prevent a small proportion of CP. Both of these interventions occur very early and require health professionals to be mindful of CP as a potential outcome that could be prevented or cured. With advances in medical, public health, and allied health research, the likelihood of further breakthroughs are probable.

Further research is required to determine why infants born at term, not at “high risk” of CP in the newborn period go on to develop CP. Health professionals need to be aware that 45%

of all CP falls into this category. Therefore we recommend prompt response to parental concerns with screening and assessments as outlined, followed by immediate referral for intervention for those infants then considered “at risk.”

Premature and term infants with brain injury identified on MRI are at high risk of CP. We have identified pathways which make recognizing “at high risk” of CP easier for health professionals. We propose a change in diagnostic practice, a shift away from referral for intervention following a formal (most often late) description to one of referral when an infant is “at high risk” of CP. This will provide the opportunity for targeted research in early intervention, thus providing optimal outcomes for children with CP.

## ACKNOWLEDGMENTS

Many thanks to the families that participate in CP Registers and research throughout the world, the clinicians who work in this important area, and Dr. Monique Hines for her fine editorial skills. This research was conducted at Cerebral Palsy Alliance Research Institute, The University of Notre Dame, Australia.

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## Chapter 3 | Study 2 META-ANALYSIS OF EARLY ENVIRONMENTAL ENRICHMENT TRIALS

### PUBLICATION

**Morgan C**, Novak I, Badawi N. Enriched environments and motor outcomes in cerebral palsy: systematic review and meta-analysis. *Pediatrics*. 2013; 132(3): e735-46.

Early intervention (EI) has been espoused as the standard of care for children at high risk of neurodevelopmental disability since the 1990s with the introduction of the “Individuals with Disabilities Education Improvement Act (IDEA)” in the USA. The aims of EI are broad and are based on the principles of neuroscience, which highlight the importance of intervening in the early years to optimise neuroplasticity mechanisms. For infants with brain lesions, the role of experience - dependent plasticity is significant.

This paper explores the effect of a known “active ingredient” for recovery in animal studies – environmental enrichment. The evidence for the effect of environmental enrichment in programmes designed for infants and very young children with CP is summarised systematically and data from five studies combined to demonstrate a small positive effect of environmentally enriching interventions on infant motor outcomes.

### Author Contributions

CM and IN were involved in quality assessment, data extraction, data analysis, and manuscript preparation; NB was involved in quality assessment and manuscript critique.

All authors were involved in study conception and design, interpretation of data, critical revision, and final approval of the submitted manuscript.

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## **Enriched Environments and Motor Outcomes in Cerebral Palsy: Systematic Review and Meta-analysis**

Catherine Morgan, Iona Novak and Nadia Badawi

*Pediatrics* 2013;132:e735; originally published online August 19, 2013;

DOI: 10.1542/peds.2012-3985

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/132/3/e735.full.html>

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# Enriched Environments and Motor Outcomes in Cerebral Palsy: Systematic Review and Meta-analysis

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## KEY WORDS

cerebral palsy, infants, enrichment, motor learning

## ABBREVIATIONS

CIMT—constraint-induced movement therapy  
COPCA—Coping with and Caring for Infants with Special Needs, CP, cerebral palsy  
EE—environmental enrichment  
GMFCS—Gross Motor Function Classification System  
NDT—neurodevelopmental therapy  
PDI—Psychomotor Developmental Index  
PEDI—Pediatric Evaluation Disability Inventory  
PVL—periventricular leukomalacia  
QUEST—Quality of Upper Extremity Skills Test  
RCT—randomized controlled trial

Ms Morgan and Dr Novak were involved in quality assessment, data extraction, data analysis, and manuscript preparation; Dr Badawi was involved in quality assessment and manuscript critique. All authors were involved in study conception and design, interpretation of data, critical revision, and final approval of the submitted manuscript.

[www.pediatrics.org/cgi/doi/10.1542/peds.2012-3985](http://www.pediatrics.org/cgi/doi/10.1542/peds.2012-3985)

doi:10.1542/peds.2012-3985

Accepted for publication Jun 20, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** Ms Morgan is personally supported by an NHMRC/Cerebral Palsy Foundation Doctoral Scholarship.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

## abstract

**BACKGROUND AND OBJECTIVES:** Neuroplasticity evidence from animals favors an early enriched environment for promoting optimal brain injury recovery. In infants, systematic reviews show environmental enrichment (EE) improves cognitive outcomes but the effect on motor skills is less understood. The objective of this review was to appraise the effectiveness evidence about EE for improving the motor outcomes of infants at high risk of cerebral palsy (CP).

**METHODS:** A systematic review was conducted. Cochrane Central Register of Controlled Trials (PubMed), Cumulative Index to Nursing and Allied Health Literature, Education Resource Information Center, SocINDEX, and PsycINFO databases were searched for literature meeting inclusion criteria: randomized controlled trials; high risk of /diagnosis of CP; >25% participants ≤2 years; parent or infant interventions post-discharge; and motor outcomes reported. Data were extracted using the Cochrane protocol regarding participants, intervention characteristics, and outcomes. Methodological quality was assessed using risk of bias assessment and GRADE.

**RESULTS:** A total of 226 studies were identified. After removing duplicates and unrelated studies, 16 full-text articles were reviewed, of which 7 studies met inclusion criteria. The risk of bias varied between studies with the more recent studies demonstrating the lowest risk. Enrichment interventions varied in type and focus, making comparisons difficult. A meta-analysis was conducted of studies that compared enrichment to standard care ( $n = 5$ ), and totaled 150 infants. A small positive effect for enrichment was found; standardized mean difference 0.39 (95% confidence interval 0.05–0.72;  $I^2 = 3\%$ ;  $P = .02$ )

**CONCLUSIONS:** EE looks promising for CP, and therefore high-quality studies with well-defined EE strategies are urgently required. *Pediatrics* 2013;132:e735–e746

Children with cerebral palsy (CP) reach ~90% of their gross motor potential by age 5 and even younger for the more severely impaired,<sup>1</sup> so effective interventions for optimizing early motor development are vital. As with typically developing children, the first 2 years are critically important for cognitive and motor development<sup>2</sup> because the brain is experiencing continuous spontaneous plasticity. Pediatricians, who are responsible for making the diagnosis of CP and referral to rehabilitation, therefore require up-to-date evidence about effective early interventions for children with CP.

The value of enriched environments in enhancing brain recovery at both structural and chemical levels has been repeatedly demonstrated in animal studies.<sup>3,4</sup> Effects of enrichment include improved memory and motor function.<sup>4</sup> Replication of animal data findings within humans is still undergoing experimentation, with one of the early challenges being how to define an “enriched human environment.” No single agreed definition of environmental enrichment (EE) in human infants exists. In animal studies, an EE is defined as an environment that facilitates enhanced cognitive, motor, and sensory stimulation.<sup>4</sup> Although there are no agreed parameters for enrichment, these animal housing conditions typically include high levels of complexity and variability with arrangement of toys, platforms, and tunnels being changed every few days to promote motor learning and memory. Researchers have postulated that it is the voluntary and challenge aspects of these environments that are crucial. Animals are not forced to perform activities; rather their engagement with the environment is active and playful.<sup>5</sup> The motor opportunities afforded by EE are a critical success factor. An intriguing theoretical question is whether an EE where an animal

can practice a task and engage in any amount of physical exercise can be actually distinguished from specific motor training, as with humans. Some animal researchers consider training a discrete intervention, whereas others include training as a “rehabilitative enrichment” component of the EE.<sup>6</sup> Either way, EEs offer opportunity for motor learning and “training,” and for the purposes of this article we considered training inclusive of environmental adaptations to enhance training, as 1 form of motor-specific enrichment.<sup>7</sup> Because no agreed definition exists, the findings of this review must be interpreted with attentiveness to the definition we posed from literature.

Animal EE ideas are difficult to replicate within human experiments because humans experience an individualized level of complexity and variability within their daily lives. In addition, unlike animals, human infants cannot voluntarily access their environment because motor maturation occurs later; for example, ambulation is not present at birth. Consequently infants are dependent on their parents for access to both generalized and motor-specific EE. Much more is known about the negative impact of deprivation on child development, inferring that EE and activity-dependent plasticity are vital.<sup>8–11</sup> Well-understood examples include the following: (1) institutionalized children within deprived environments display intellectual quotients 20 points lower than peers,<sup>12,13</sup> which is reversible when EE is applied within orphanages<sup>13</sup>; (2) children living in chronic poverty experience slower growth, worse health, and lower intellectual ability unless EE protective factors are in place (eg, parental responsiveness and acceptance, availability of learning materials, safe play areas, and a variety of experiences)<sup>14</sup>; (3) typically developing children experience delayed sitting skills from parents conscientiously following

the Sudden Infant Death Syndrome “back to sleep” program, which deprives children of experiences in prone, but is fortunately remediable<sup>15</sup>; and (4) typically developing children experience delayed walking from regular use of infant walkers, whereas Jamaican infants walk earlier owing to parental handling techniques.<sup>16,17</sup> It should be noted that these latter examples have only a short-term influence on motor development in typically developing children, and it is not known if these environmental influences benefit or disadvantage infants with motor disorders in any way. Motor-enrichment interventions have recently been trialed in preterm and typically developing infants. Reaching training delivered by caregivers to their preterm infants was able to partially ameliorate the delayed reaching skills often observed in the preterm population.<sup>18</sup> Similarly, training parents to practice specific motor tasks with typically developing infants accelerated the rate of motor development in both the short and long term.<sup>19,20</sup>

In the small amount of literature about the benefits of EE for infants at risk for brain injury, we know that premature infants demonstrate neurobehavioral benefits from sensory-specific EE activities, such as massage<sup>21</sup> and music.<sup>22</sup> Developmental care interventions for premature infants have been shown to deliver modest short-term gains, but with some trials showing no benefit at all.<sup>23</sup> Some programs, such as The Newborn Individualized Developmental Care and Assessment Program, a sensory-specific EE and cue-based intervention for high-risk infants, has been shown to positively influence brain function and motor development.<sup>24</sup> Generic EE via early interventions, such as the Head Start program,<sup>25</sup> provide cognitive benefits short-term, especially for infants from lower socioeconomic backgrounds whose risk of



environmental deprivation is higher. Similarly, systematic reviews show favorable short-term cognitive benefits from generic EE programs offered to premature infants.<sup>26,27</sup> Because only ~8% to 15% of premature infants will go on to have CP,<sup>28</sup> it is not clear whether interventions aimed at preterm infants will have clear benefits for infants with CP. In contrast, “traditional” physical and occupational therapy early-intervention approaches, such as neurodevelopmental treatment (NDT), have not been shown to be effective in improving motor outcomes in infants or older children with CP, despite the theoretical possibility of providing sensory-enrichment cues for learning motor skills.<sup>29,30</sup>

Given that optimization of neuroplasticity is the aim of all rehabilitation, it is important for those who deliver early-intervention services to understand the parental and EE-intervention role that in turn is informed by knowing the important components of EE for infants with brain injury. Indeed, the

importance of the role of parents in providing optimal home environments for at-risk infants,<sup>31</sup> as well as arranging opportunities for motor training, have been highlighted in recent reviews.<sup>32</sup>

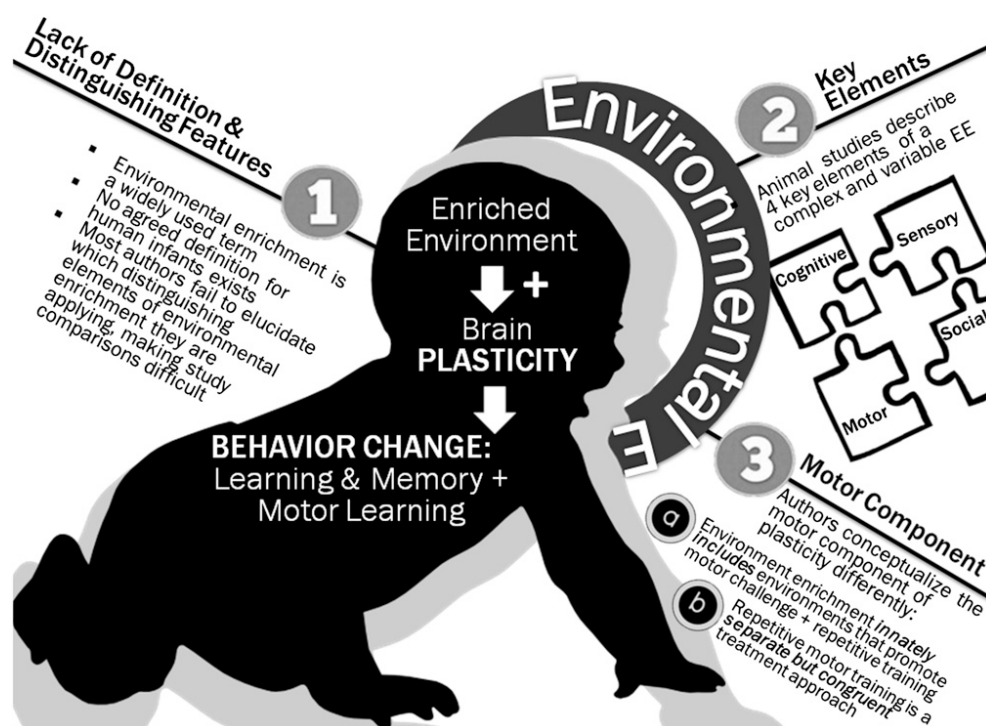
Because interventionists use the term EE without definitional or procedural precision, it is important to be clear that not all therapy interventions are enriching. In some standard care interventions, manual handling techniques are applied with the child’s role being largely passive. This contravenes animal EE definitions, in which active exploration of complex and variable environments is required. For the purposes of this review and in the absence of an agreed infant EE definition, we proposed an operational definition of infant EE, consistent with the animal literature (Fig 1). Infant EEs are interventions that aim to enrich at least 1 of the motor, cognitive, sensory, or social aspects of the infant’s environment for the purposes of promoting learning. Examples include interventions aiming

to enhance parent-infant interaction, educate parents about assisting their child’s skill development, provide opportunities for active motor learning (self-generated motor activity) by adapting the physical and play environment, or provide comprehensive programs aimed at enrichment across a number of domains.

The purpose of this study was to systematically review the evidence for the effectiveness of EE interventions (either generic EE or motor-specific EE; eg, motor training) for infants at very high risk of CP, which explicitly sought to improve motor outcomes.

## METHODS

The method used was a systematic review and meta-analysis with reporting according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.<sup>33</sup> A comprehensive search was conducted of the following databases between May and August 2011 and updated in



**FIGURE 1**  
Environmental enrichment—infancy.

May 2012: The Cochrane Library, including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (inclusive of PubMed); the Cumulative Index to Nursing and Allied Health Literature; PsycINFO; Education Resource Information Center; and SocINDEX.

## Types of Studies

Included studies were randomized controlled trials (RCTs). Systematic reviews were also retrieved but not appraised as per conventions. Controlled studies and studies in languages other than English were excluded.

## Types of Participants

Participants were either infants with a confirmed diagnosis of CP of any subtype or severity, or infants designated “at high risk” of CP using the best predictive tools available, namely, abnormal general movements (absent fidgety) or abnormal brain imaging (cranial ultrasound or magnetic resonance imaging). Studies were included in which 25% of participants were 2 years of age or younger at the time of study enrollment.

## Types of Interventions

### EE Interventions

EE interventions of interest were those in which the infant's environment was enriched via parent training or coaching in parent-infant interaction or in various stimulation activities, specifically those for motor learning; or where the physical environment was modified, adapted, or constructed to enable motor skill attainment; or where therapists provided intense, targeted motor skill practice aimed at enhancing plasticity. Interventions that solely focused on enriching parent well-being for improving parent outcomes but not for improving child motor outcomes were excluded. The effects of regular parental caregiving were not specifically teased

out for either the EE or comparison group, because if effective for promoting motor development, we would expect as a function of randomization that positive parental caregiving was evenly distributed between both groups. Studies of “NDT plus” were included in the EE categorization if, and only if, the added elements of the intervention (ie, the “plus” component) clearly involved EE.

### Comparison Interventions

Comparison interventions were those deemed “standard care” as provided by physiotherapists and included traditional approaches, such as NDT or Vojta. NDT and Vojta were not considered enrichment interventions by our definition, because NDT and Vojta, despite modernization, continue to fundamentally focus on passive therapist-delivered facilitation and inhibition (therapeutic handling).<sup>34</sup> In contrast, EE approaches deliberately minimize handling to promote active child-generated muscle activation and movement. Interventions that included handling or positioning embedding into daily routines were regarded as largely passive interventions and were thus treated as non-EE interventions from standard care, on the basis that these treatment ideas originated from NDT.

## Types of Outcome Measures

Outcome measures of interest were those that assessed progress in motor skill acquisition at any time point after intervention and as either a primary or secondary measure. To improve homogeneity, meta-analysis was conducted using only data collected at time points immediately at the end of the intervention period.

## Search Terms

The following Population, Intervention, Comparison, Outcome search terms were used: P = cerebral palsy OR neonatal stroke OR intraventricular hemorrhage

OR brain injury OR hypoxic ischemic encephalopathy OR newborn encephalopathy OR periventricular leukomalacia (PVL); I = environment OR enriched environment OR enhanced environment OR home environment OR nurture OR parenting OR parent training OR parent coaching OR caregiving OR shaping OR stimulation OR intensive task practice; C = nil; O = motor development OR motor skills OR motor learning OR motor outcome. Filters applied during the searching were “infants 0–23 months” and articles in English. Abstracts from conferences and dissertations were excluded. Additional hand searching was conducted from reference lists and field expert recommendations.

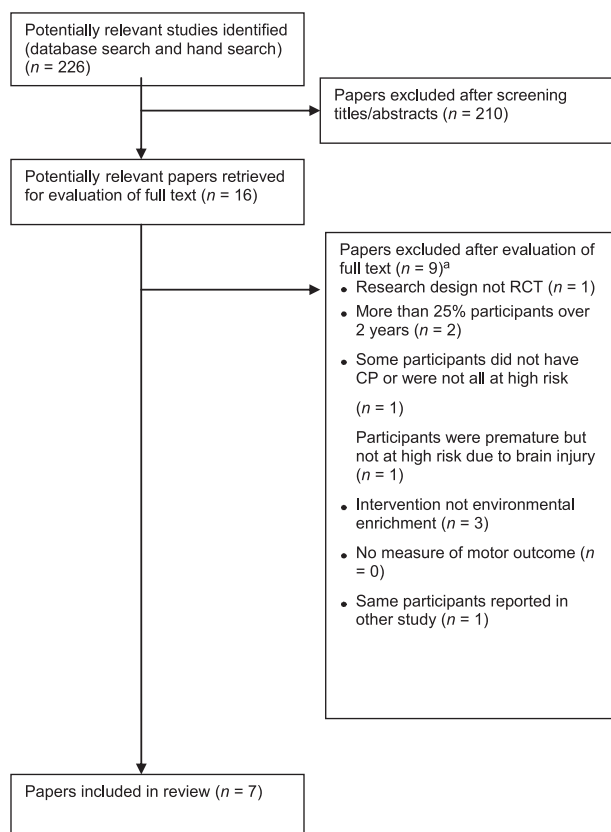
## Selection of Studies

Two authors (C.M. and I.N.) independently screened all titles and abstracts, identified articles, and excluded irrelevant citations. Full-text articles of all potentially relevant articles were obtained and assessed for eligibility. Ninety-five percent agreement was reached; disagreement was resolved through discussion and consensus. The criteria for study exclusion are documented in Fig 2.

## Data Extraction and Management

A data extraction tool based on the Cochrane guidelines<sup>35</sup> was used by 2 authors (C.M. and I.N.). The following data were extracted: study design; inclusion and exclusion criteria; participant characteristics, including the diagnosis of CP or “high risk of CP”; number of participants; age and gender of participants; characteristics of the intervention and comparison interventions, including treatment approaches and duration, frequency, and intensity of intervention; details of cointerventions plus compliance with treatment protocol; motor outcomes; methods used to measure change in



**FIGURE 2**

Flow diagram. <sup>a</sup>Articles may have been excluded for failing to meet >1 inclusion criterion.

motor function; mean scores and SDs of outcomes; and direction of effect for motor outcome. We contacted authors of included studies when there was incomplete reporting of data. All authors contacted were able to provide the missing data requested.

### Quality of Studies and Risk of Bias

The methodological quality of the included studies was assessed by using the Cochrane risk of bias recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*<sup>35</sup> and is summarized in Table 2.

### Analyses

Meta-analysis was conducted for the studies that were clinically homogeneous. Data were analyzed by using Review Manager 5 (RevMan; Computer program Version 5.1. Copenhagen: The

Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The  $I^2$  statistic was used to quantify the heterogeneity of outcomes and informed decisions about whether to pool data. Meta-analyses were conducted by using a random-effects model to conservatively account for the data heterogeneity. The mean differences in motor outcomes were pooled for each study to provide a summary estimate of the effectiveness of EE interventions. For all continuous outcomes with different units, effects were expressed as standardized mean differences and 95% confidence intervals.

### RESULTS

The electronic searches, citation tracking, and reference list searches elicited 226 references after 9 duplicates were removed. After screening titles and abstracts, 16 studies were

identified, and after inspecting the full-text articles, 7 studies met full inclusion criteria. Reasons for exclusion are summarized in Fig 2.

### Included Studies

Across the 7 included studies there were a total of 328 participants (Table 1). Three studies<sup>36–38</sup> investigated the effects of EE interventions (as per our definition) on very young hospitalized infants with brain injuries and at high risk of CP and followed their progress post discharge. The remaining 4 studies<sup>39–42</sup> investigated EE interventions (as per our definition) in children older than 1 year with a confirmed diagnosis of CP. The features of EE interventions varied considerably among the studies. Six studies provided part of the EE intervention via parent training or coaching. This included ways of interacting with their infant,<sup>36–38</sup> strategies for modifying the physical environment for motor task practice, and providing frequent opportunities for task practice.<sup>39,40,42</sup> Only 1 study did not actively train parents but encouraged them to “use newly acquired skills when the therapist was not present.”<sup>41p306</sup>

### Methodological Quality and Risk of Bias in Included Studies

The methodological quality and risk of bias in the 7 included studies were variable, with a tendency for the more recent studies to be of the highest quality and at the lowest risk of bias (Table 2). Three studies used adequate methods for generating the randomization sequence but 4 were unclear. Three studies used adequate methods to conceal allocation. Blinding of participants and therapists was not possible in any of the studies because of the “hands-on” and thus visible nature of the intervention. Five of the studies used assessors who were blinded to group allocation and 4 studies had

**TABLE 1** Summary of Included Studies

Study	Participants	Design and Intervention	Enrichment Used	Provider	Outcome Measures	Results
Badr et al <sup>36</sup> (2006)	n = 62	RCT	Cognitive enrichment: CAMS program	Nurse	Motor: Bayley PDI	No difference between groups, Bayley PDI fell in both groups. Confounded by 30% attrition rate.
	Age: 0 mo	Aim: Enhance cognitive and sensorimotor development	Motor enrichment: Training parent in various stimulation activities for motor learning		Other: Bayley MDI; NCAFS; NCATS; PSI	NOTE: Data reanalyzed in 2009, showing significant difference between groups favoring enrichment
	38M; 24F	Gp1 = Enriched intensive stimulation using CAMS (Curriculum and Monitoring System)				
	100% high risk CP	Gp 2 = Standard care				
Law et al <sup>39</sup> (2011)	n = 128	RCT	Motor enrichment: Changing the environment to enable goal attainment	Physiotherapist or occupational therapist	Motor: GMFM, PEDI, joint ROM	No significant difference between groups. Both groups improved equally on the PEDI and GMFM
	Age: 12-71 mo (34% ≤2) <sup>a</sup>	Aim: Improve performance on functional tasks and mobility and increase participation in everyday tasks	Parent coaching in problem solving child movement difficulties		Other: APGP; FES	
	79M; 49F	Gp 1 = context-focused therapy (therapeutic intervention aimed at task ± enriching environment)	Intensive, customized, and variable task practice			
	100% CP	Gp 2 = child-focused therapy (therapeutic intervention aimed at child only; may include intensive task practice)				
Nelson et al <sup>37</sup> (2001)	n = 37	RCT	Social enrichment: Training parent-infant interaction	Research assistant, then parent	Motor: Bayley PDI	No significant difference between groups on Bayley at 12 mo. Confounded by >25% attrition rate. Best predictor of motor outcome was presence of PVL
	Age: 0 mo	Aim: Reduce incidence of handicap	Sensory enrichment: auditory/tactile/visual/Vestibular		Other: Bayley MDI; Dyadic Mutuality Code; NCAFS	
	18M; 19F	Gp1 = Enrichment via multisensory stimuli + standard care				
	100% high-risk CP	Gp 2 = Standard care				
Ohgi et al <sup>38</sup> (2004)	n = 23	RCT	Social enrichment: Training parent-infant interaction	Neonatal Behavioral Assessment Scale certified examiner	Motor: Bayley PDI	No significant difference between groups on motor outcomes at 6 mo
	Age: 0 mo	Aim: Facilitate infant development			Other: Bayley MDI; NBAS; STAI; LCC	
	17M; 6F	Gp1 = Enrichment via training of mother-infant interaction + handling and developmental support using NDT principles				
	100% high-risk CP	Gp 2 = Standard care				

TABLE 1 Continued

Study	Participants	Design and Intervention	Enrichment Used	Provider	Outcome Measures	Results
Palmer et al <sup>40</sup> (1988)	n = 48  Age: 12–19 mo  36M;12 F	RCT  Aim: Promote cognitive and motor development  Gp1 = Enriched intensive stimulation using <i>learninggames</i> (cognitive, sensory, language and motor activities) for 6 mo followed by 6 mo NDT Gp 2 = Standard care (12 mo NDT)	Cognitive/social enrichment: Training parent in various stimulation activities Motor enrichment: Changing the environment to enable goal attainment Intensive, customized and variable task practice	Child development specialist	Motor: Bayley PDI  Other: Bayley MDI; Vineland	Significant difference between the groups favoring enrichment at both 6 and 12 mo
Taub et al <sup>41</sup> (2004)	100% CP n = 18  Age: 7–96 mo (50% ≤2)	RCT  Aim: Improvement in motor function of affected arm Gp1 = Enriched intensive task practice via shaping with constraint Gp 2 = Standard care (conventional PT/OT)	Motor enrichment: Intensive, customized and variable task practice	Occupational therapist, physiotherapist or PT assistant	Motor: EBS, PMAL, TAUT	Significant difference between the groups favoring enrichment Note: Cochrane review in 2007 details QUEST scores on this group not reported in the article
Wallen et al <sup>42</sup> (2011)	13M; 5F 100% CP n = 50  Age: 19–94 mo (34% ≤2) <sup>a</sup> 27M; 23F	RCT  Aim: Improve performance in ADL tasks Gp 1 = Enriched intensive task practice, mCIMT plus home program Gp 2 = Enriched Intensive OT plus home education program	Motor enrichment: Training parent in various stimulation activities for motor learning Intensive, customized task practice	Occupational therapist	Motor: AHA, PMAL-R  Other: COPM; GAS	No significant difference between groups. Motor outcomes improved equally in both groups

AHA, Assisting Hand Assessment; APOP, Assessment of Preschool Children's Participation; COPM, Canadian Occupational Performance Measure; EBS, Emerging Behaviors Scale; FES, Family Empowerment Scale; GAS, Goal Attainment Scaling; GMFM, Gross Motor Function Measure; Gp 1, experimental group; Gp 2, control group; LCC, Lack of Confidence in Caregiving; mCIMT, modified Constraint-Induced Movement Therapy; NBAS, Neurobehavioral Assessment Scale; NCAFS, Nursing Child Assessment Feeding Scale; NCATS, Nursing Child Assessment Teaching Scale; PMAL, Pediatric Motor Activity Log; PMAL-R, Pediatric Motor Activity Log Revised; PSI, Parenting Stress Index; STA, State Trait Anxiety Inventory; TAUT, Toddler Arm Use Test.

<sup>a</sup> Confirmed with author.

**TABLE 2** Cochrane Risk of Bias Assessment

Study	1	2	3	4	5	6	7
Badr et al <sup>36</sup> (2006)	?	?	—	+	—	+	—
Law et al <sup>39</sup> (2011)	+	+	—	+	+	+	+
Nelson et al <sup>37</sup> (2001)	?	?	—	—	—	+	+
Ohgi et al <sup>38</sup> (2004)	+	—	—	+	+	+	+
Palmer et al <sup>40</sup> (1988)	?	?	—	+	+	+	+
Taub et al <sup>41</sup> (2004)	?	+	—	—	—	—	—
Wallen et al <sup>42</sup> (2011)	+	+	—	+	+	+	+

The Cochrane Risk of Bias assessment domains addressed are the following: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other bias. +, low risk of bias; —, high risk of bias; ?, unclear.

adequate follow-up. Only 1 study selectively reported outcomes and 5 studies were free of other bias because they provided full statistical reporting.

### Effects of Interventions on Motor Outcomes

Five of 7 included studies compared an EE intervention with standard care and were clinically homogeneous for meta-analysis (ie, compared EE with standard care, and used the Bayley Psychomotor Developmental Index [PDI] [4/5] trials). Standard care was not clearly described in terms of the treatment approaches in use or the intensity of intervention provided. Two of the 7 studies compared 2 different types of EE interventions (as per our definition) head to head.<sup>39,42</sup> In the study by Law et al,<sup>39</sup> both the context-focused group and the child-focused group enlisted intensive task practice as an EE feature. What differentiated the groups was that the context-focused intervention also included parent training and environmental adaptations to promote functional skill attainment. Likewise, Wallen et al<sup>42</sup> compared modified constraint-induced movement therapy (CIMT) with an intensive occupational therapy approach in which both groups received intensive task practice and parent training aimed at EE.

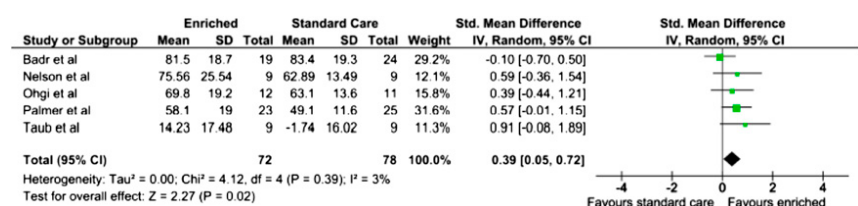
The 5 studies that compared EE with standard care were included in the meta-analysis. Data imputed into the analyses were motor outcomes captured at the immediate cessation of

treatment. Motor outcome data were pooled from 4 studies using the Bayley PDI<sup>43</sup> and 1 study using the Quality of Upper Extremity Skills Test (QUEST).<sup>44</sup> For the study by Nelson et al,<sup>37</sup> only the values reported on infants with a central nervous system injury were included within the meta-analyses, which was possible because these figures were reported separately from infants without central nervous system injury. Data from the 6-month point were used from the Palmer et al<sup>40</sup> study because infants in the experimental group received the enrichment intervention only during the first 6 months and then after this they were prescribed maintenance NDT for the next 6 months. QUEST values for the Taub et al<sup>41</sup> trial were used, as this was the only motor outcome measure used in this trial for which appropriate psychometrics were available. These values were retrieved from the Cochrane Review by Hoare et al.<sup>45</sup> When combined, the 5 studies included a total of 150 participants. The standard mean difference was 0.39 (95% confidence interval 0.05–0.72;  $I^2 = 3\%$ ;  $P = .02$ ), indicating a small positive effect favoring

enrichment over standard care (Fig 3: forest plot).

## DISCUSSION

The aim of this systematic review was to determine the effect of EE intervention programs on the motor outcomes of infants who were 2 years and younger with a high risk or diagnosis of CP, compared with standard care. This is the first systematic review and meta-analysis that has attempted to define and measure the effect of EE on motor development of infants with CP. Previous systematic reviews have focused more broadly on motor and cognitive outcomes in preterm populations<sup>27</sup> or those at risk for a broader range of developmental disorders.<sup>46,47</sup> In these previous studies, favorable cognitive outcomes programs have been consistently demonstrated for a range of early-intervention programs, but motor outcomes rarely improve. Five studies with sufficient homogeneity for meta-analysis were found, which indicated good-quality evidence for a very small but favorable benefit from enrichment interventions in improving motor outcomes for infants with CP. The studies were all RCTs (ie, high levels of evidence, of medium-high quality, and varying levels of risk of bias). The entire body of evidence for EE improving motor outcomes in infants with CP was graded as moderate quality (ie, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate).<sup>48</sup> Nevertheless, our study makes a new and unique contribution to



**FIGURE 3**  
Forest plot.

the literature by highlighting ways to improve motor outcomes at an early age. Unfortunately, it was not possible to draw conclusions about the contributions of the varying components of EE because of the high levels of intervention and participant heterogeneity among the studies. The studies varied in severity of motor impairment, initial degree of risk for CP, the type of EE used, the intervention duration, the involvement of parents, and the motor assessments used. The meta-analysis appears, however, to indicate that enrichment is beneficial, despite differences in child attributes and “favorable” parent characteristics, as conceivably any differences would have been distributed evenly across EE and non-EE groups owing to randomization.

The 2 studies that commenced with newborns were unable to demonstrate favorable motor outcomes for the experimental groups. Although reasons were explored in each publication, we also concluded that these studies were inadvertently underpowered because only a small proportion of participants ultimately ended up with a CP diagnosis. In other words, because most of the participants in both groups were healthy or mildly affected, intervention would be unlikely to affect their results. Infants who have normal or milder motor impairments will unmistakably score better on norm-referenced tools, such as the Bayley PDI, than will infants with CP. Potentially grouping motor-impaired infants with those whose delay is simply related to prematurity does not allow identification of aspects of the interventions that may have been effective for the different diagnoses. In addition, it has been suggested in earlier reviews that norm-referenced tools, such as the Bayley PDI, may not be sensitive enough to measure change in infants with CP.<sup>46</sup> The 3 infant studies used different inclusion criteria for defining risk of CP, which is likely

to further explain the nil findings. For example, Badr et al<sup>36</sup> curiously excluded a subgroup of infants with the highest risk for CP (eg, Grade IV intraventricular hemorrhage with PVL), but the remaining study group still had some risk factors for CP.

Not surprisingly, only a small percentage of infants were then diagnosed with CP at follow-up. Nelson et al<sup>37</sup> reported a final CP diagnostic rate of 44% to 67%, dissolving the study power. None of the studies included infants younger than 12 months who had not been sick in the neonatal period. This is an interesting finding, and supports the authors' experience that almost half of infants at risk for CP are not being referred for therapy services until closer to their first birthday.<sup>28</sup> Another identified limitation in 2 of the infant studies (Nelson et al,<sup>37</sup> Ohgi et al<sup>38</sup>), was that the authors ceased intervention before, or at 6 months of age, before the average age at which CP is commonly diagnosed. It is therefore unclear whether ongoing intervention of different types (ie, EE versus no EE) would have changed the results, as the complexity of motor demands increases over time and children with CP tend to fall farther and farther behind.

Several studies had to be excluded from this review, because they did not meet the inclusion criteria of a sample at high risk of CP; most notably, an RCT that compared the parent coaching intervention “Coping with and Caring for Infants with Special Needs” (COPCA), with standard care. In the COPCA study, there were no differences between the groups with respect to motor outcomes, which should have perhaps been expected given that <25% of participants were eventually diagnosed with CP. Thus, for the most part, authors were comparing healthy infants with healthy infants. Post hoc analysis of infants with CP revealed a positive correlation between PEDI

scores and elements of the COPCA approach.<sup>49,50</sup>

In the subsequent years since many of these clinical trials have been conducted, the field has learned a great deal more about how to precisely identify infants who are most at risk for CP. It is now possible to identify those infants at risk for CP with a high degree of accuracy using the General Movements Assessment plus imaging.<sup>51,52</sup> Abnormal general movements (“absent fidgety”) at 3 months corrected age predicts CP with a sensitivity of  $\geq 92\%$  (specificity  $\geq 82\%$ ).<sup>53</sup> In light of our study findings, using best practice tools to identify those infants at risk for CP and to tease them apart from those at risk for general delay is very important, as EE interventions can be specifically targeted at motor development if this is expected to be impaired. Also, earlier intervention instituted at a time of greater brain growth and plasticity is likely to be associated with a stronger beneficial effect.

Of the 4 studies that included infants with a confirmed CP diagnosis, the severity of the motor impairment varied, which is known to be a covariate for explaining study findings.<sup>54</sup> Only 1 study (Law et al<sup>39</sup>) included children from all Gross Motor Function Classification System (GMFCS) levels. The Taub et al<sup>41</sup> and Wallen et al<sup>42</sup> studies included only children with hemiplegia (usually GMFCS I–II) and Palmer et al<sup>40</sup> applied their enrichment intervention to a subgroup of children with diplegic CP. Although the Palmer et al<sup>40</sup> study predates the invention of GMFCS, it is clear from the description of the participants that almost all infants had motor skills that fall into GMFCS I to III categories (ie, were certain to be ambulatory). Broadly speaking, the interventions described in these 4 studies all involved motor task practice customized to the child, delivered by



a professional (therapist or teacher) and reinforced by tailored home practice. Interestingly, these 4 of the 7 studies were the studies that showed a positive trend favoring EE.

The study by Law et al<sup>39</sup> that compared 2 different EE interventions head-to-head found both approaches were equally effective. Law et al's<sup>39</sup> findings are consistent with other studies of functional therapy or task-based training EE approaches known to be effective in older children.<sup>55,56</sup> In line with the International Classification of Functioning, Disability, and Health, functional therapy or task-based training EE approaches deliberately consider the impact of the environmental context in the design and implementation of therapy. The difference with Law et al's<sup>39</sup> context-focused study is that 2 novel approaches are compared: "hands off and hands on." In a typical clinical situation it is unlikely that only child-focused ("hands on") or context-focused therapy ("hands off") would be provided. A combination of strategies that target both the child and the context is more likely. Our review did not locate any studies that used these functional motor learning, goal-driven, and environmentally enriching approaches for infants with little or no motor repertoire. This remains a gap in literature, warranting further study. Wallen et al<sup>42</sup> and Taub et al<sup>41</sup> used different models of CIMT as a form of EE (as per our definition). It is the motor-learning strategies, or shaping, that co-occur with use of a constraint that

make this approach motor-specific enrichment. The 2 studies used quite different approaches with variations in intensity and the type of constraint used. However, both experimental groups offered a similar total amount of intervention (mean 119 hours) but over different durations (3 weeks or 10 weeks). Although the study by Taub et al<sup>41</sup> demonstrated impressive motor outcomes for the constraint group, a subsequent Cochrane review outlines substantial sources of bias in this study.<sup>45</sup> In contrast, both groups in the Wallen et al<sup>42</sup> study used an EE approach in which the experimental group constraint was the "added extra." Motor outcomes improved in both groups. It may be that the consistent motor-learning/task-practice approach is the key component of these studies.

### Limitations of This Review

Some of the included studies in this review did not provide adequate descriptions of standard care interventions, resulting in the possibility that enrichment activities were indeed part of these comparison groups, which would ultimately dissolve statistical power. It is, however, our experience that standard care for young infants is typically a "wait-and-see" approach, which mostly involves active monitoring of the infant over the first 12 months. It is also possible that because of the definition of EE used, intervention studies that actually offered enrichment were omitted. This confounder was minimized by clearly defining EE

and features of enrichment, using extensive hand searching and using search terms indicative of the early intervention field. In particular, opportunities for motor task practice were included within the definition of EE, as it seems evident that for infants to develop motor skills, opportunities must be provided within their learning environment. However, other definitions of EE may single out EE from task practice opportunities. Future studies should therefore be careful to detail the approaches and strategies in use, the frequency and intensity of intervention of all groups, and account for the effect of cointerventions. In particular, the breakdown of the approach and the extent of parent involvement should be specified to advance our understanding of human EE.

### CONCLUSIONS

Enrichment interventions to improve motor outcomes in infants at high risk of CP appear promising. Therefore, more high-quality, low-bias, large-sample, longitudinal RCTs that examine the effects of motor task practice with deliberate attention to environmental enrichment via appropriate parent training and a variety of stimulating opportunities for learning are urgently needed. Researchers also need to use the best available evidence to accurately identify those at the highest risk of CP for inclusion in these trials to ensure adequate study power.

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## Enriched Environments and Motor Outcomes in Cerebral Palsy: Systematic Review and Meta-analysis

Catherine Morgan, Iona Novak and Nadia Badawi

*Pediatrics* 2013;132:e735; originally published online August 19, 2013;

DOI: 10.1542/peds.2012-3985

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## Chapter 4 | STUDY 3 SENSITIVITY AND SPECIFICITY OF EARLY DETECTION PUBLICATION

**Morgan C, Crowle C, Goyen TA, Hardman C, Jackman M, Novak I, Badawi N.** Sensitivity and specificity of General Movements Assessment for diagnostic accuracy of detecting cerebral palsy early in an Australian context. (Accepted for publication in *Journal of Paediatrics & Child Health* 2015)

Our literature review (Study 1) demonstrated the depth and quality of evidence available for predicting CP in high-risk infants when the *right assessment tools* are used at the *right time*. We established a network of trained general movements (GMs) assessors who continue to meet biannually to share cases and maintain inter-observer reliability. In Study 3, five sites collaborated to assess whether our network could detect CP using the General Movements Assessment with sensitivity and specificity rates similar to published European standards. Using Standards for the Reporting of Diagnostic Accuracy studies (STARD) criteria, we assessed our diagnostic accuracy in a high-risk group that included both preterm and term infants.

Our results were similar to rates previously published, confirming we were detecting CP accurately from this high-risk group of infants. Furthermore, we confirmed we could accurately detect the “right” infants for early intervention trials, which is vital to advance the evidence base in this field.

The establishment of the GMs rater network and the confirmation of diagnostic accuracy served to “set the scene” for the recruitment of infants to clinical trials (Studies 5 and 6).

### Author Contributions

CM: Co-designed study, collated and analysed data, drafted manuscript and finalised for submission and review

CC, TG, CH, MJ: Collected data and assisted in draft and revisions of manuscript

IN & NB: participated in the concept and design of the paper and revising the original and revised manuscripts

NOTE: This paper has been submitted to *The Journal of Pediatrics and Child Health*. Minor revisions were submitted, publication imminent.

# **Sensitivity and specificity of General Movements Assessment for diagnostic accuracy of detecting cerebral palsy early in an Australian context**

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## **ABSTRACT**

### *AIM*

To calculate the sensitivity and specificity of the General Movements Assessment (GMA) for estimating diagnostic accuracy in detecting cerebral palsy (CP) in an Australian context by a newly established NSW rater network.

### *METHODS*

A prospective longitudinal cross-sectional study was conducted. The GMA was blind-rated from conventional video by two independent certified raters, blinded to medical history. A third rater resolved disagreements. High-risk population screening for CP using the GMA during the fidgety period (12-20 weeks) was carried out in four neonatal intensive care units and one CP service over a 30-month period (2012-2013). Participants were 259 high-risk infants. Sensitivity and specificity values were calculated with true positives defined as a confirmed diagnosis of CP from a medical doctor.

### *RESULTS*

Of the 259 infants assessed, one-year follow-up data was available for 187. Of these, n=48 had absent fidgety (high risk for CP), n=138 had normal fidgety (low risk for CP), and n= 1 had abnormal fidgety (high risk for a neurological disorder). Of the 48 with absent fidgety movements, 39 had received a diagnosis of CP by 18 months and another 6 had an abnormal outcome. Of the n =138 normal fidgety cases, n=99 cases had a normal outcome, n= 38 had an abnormal outcome but not CP, and n=1 had CP. For detecting CP, we had a sensitivity of 98% and specificity of 94%.

### *CONCLUSION*

GMA was feasible in an Australian context and accurately identified CP with a sensitivity and specificity comparable to European standards and published neuroimaging data.

**KEY WORDS:** general movements assessment, cerebral palsy, infants

## Introduction

Cerebral palsy (CP) is defined as a group of disorders of movement and posture that results from a lesion to the developing brain(1) and is the most common physical disability of childhood. Early detection of CP is important as it allows referral to early interventions aimed at maximising motor and cognitive outcomes in children and providing support to families (2, 3).

Data from the Australian Cerebral Palsy Register shows that the average age for diagnosis of CP is 17 months although the range varies from a few weeks to 4 years of age (I. Novak, unpubl data, 2014). About half of all children diagnosed with CP have identifiable markers that enable them to be labelled “at risk” during the neonatal period, e.g. prematurity or neonatal encephalopathy (2). These infants are typically cared for in neonatal intensive care units (NICUs) and are often enrolled in follow-up programs to ascertain their long-term outcome. These programs follow protocols to monitor infants for evidence of developmental delay or disabilities, referring for early intervention once signs become apparent.

Recent systematic reviews have demonstrated that in fact CP can reliably be detected as early as 3 months post term age using Prechtl’s Qualitative Assessment of General Movements Assessment (GMA) and Medical Resonance Imaging (MRI) (4,5-6). The GMA was developed by Professor Heinz Prechtl in the early 1990s and is an assessment of the spontaneous movement patterns [“general movements”

(GMs)] of young infants(7,8). Two periods of GMs are described; the “writhing period” from preterm until 6-9 weeks post term age, and “fidgety period” from 9-20 weeks post term age(9). Normal GMs are shown to have a high correlation with a normal outcome, while abnormal GMs, in particular absent fidgety GMs (F-), are highly predictive of CP (sensitivity as high as 98% and specificity 91%,(6)). Thus the GMA is considered the reference standard for early detection of CP. Validity of the tool is established(9) and inter-rater reliability of the GMA has been repeatedly demonstrated(9-11). Importantly, a number of studies have demonstrated that the predictive validity of the GMA is superior to neuroimaging (6), while the combination of abnormal GMA and white matter injury evident on MRI has been shown to be 100% predictive of an outcome of CP in a cohort of preterm infants (13). Studies in infants with Hypoxic Ischaemic Encephalopathy (HIE) showed a high correlation between abnormal GMs and lesions of the basal ganglia and thalamus(12).

Despite the compelling psychometric data, implementation of GMA in clinical practice outside of Europe has been ad hoc and is a “know-do” evidence to practice gap. Systematic reviews on the predictive validity of the GMA have proposed that the lack of non-European data, especially outside the expert group (General Movements Trust), is a potential limitation to the generalizability of findings and possible explanation for the know-do gap(5). Use of the GMA has been growing in Australia in the last 7-8 years. Spittle and colleagues from Melbourne Australia have demonstrated sensitivity and specificity results similar to European rates in very preterm children. In addition, their work has demonstrated important associations

between neuroimaging findings and the GMA in predicting later neurodevelopmental outcomes (13-15). These important studies have focused on preterm infants, a population that make up about 30% of all CP (2). To date little published data exists on the diagnostic accuracy of the GMA for a more heterogeneous clinical population of high-risk infants in an Australian context. In 2011, a knowledge translation program to close the GMA know-do gap was implemented in New South Wales (NSW) Australia. First, European trainers were brought to Australia to remove the barrier of needing overseas rater training. Second, educational scholarships were provided to remove the costs of obtaining rater training. Third, a new rater network was established in NSW for the purpose of providing peer-to-peer support for maintaining GMA scoring reliability and troubleshooting any difficulties embedding the GMA in clinical practice. Network meetings are held twice a year and trained assessors from all participating centres present cases for blind scoring to help maintain inter-rater reliability. Between network meetings, de-identified videos are shared for blind scoring purposes to arbitrate any discrepancies.

The aim of this study was to calculate the sensitivity and specificity of the GMA for diagnostic accuracy of detecting CP at 3-5 months of age in high-risk infants, in an Australian context when scored by the NSW rater network.

## **Methods**

## Participants

Inclusion criteria: (1) All infants included were those prospectively enrolled in follow-up clinics and screened using the GMA from the study sites: 4 NICUs in NSW Australia (Westmead Hospital, the Children's Hospital at Westmead, John Hunter Children's Hospital and Royal Prince Alfred Hospital) and the Cerebral Palsy Alliance (CPA); (2) All infants were designated high-risk of poor neurodevelopmental outcome based on their medical history and /or neuroimaging by at least one member of their treating team. This included infants admitted to NICUs post surgery or with neurological risk factors (eg. severe intraventricular haemorrhage, periventricular leukomalacia, neonatal stroke), hypoxic ischaemic encephalopathy (stage II-III), or due to prematurity (ie. <29 weeks, one unit enrolled <32 weeks); or infants referred to CPA with motor delay or neurological signs suggestive of CP. Recruitment via voluntary participation was offered to all infants meeting the inclusion criteria, unless there was a competing concurrent study in which case they were offered enrolment to both studies, with researchers respecting the parent's choices. Exclusion criteria: Nil.

## Methodology

High-risk population screening for CP was conducted at study sites, predominantly in the NICU follow-up clinic over a 30-month period, resulting in a prospective longitudinal and cross-sectional study. The CPA received referrals from concerned parents and professionals in the community to screen infants for signs of CP.

Instrument: General Movements Assessment



Infants were assessed during the fidgety movement period at the developmental follow-up clinic or in the family home. Since GMs in the fidgety period are the most predictive for a later diagnosis of CP, our outcome of interest, we focused on results from this GMA period. GMAs for 259 infants were collected on conventional video following the protocol outlined by Einspieler et.al (9).

All study sites used certified GM assessors to score the videos blinded to medical and clinical history. Although all sites had certified blind raters there was a number of minor pragmatic practice variations across the study sites in relation to the processes for arranging the scoring. Despite uniformity being preferable, in the clinical setting local variations was deemed allowable as the greater knowledge translation goal was for as many raters as possible to be using the GMA and all study sites to develop feasible and acceptable local processes that led to routine GMA use. For instance, one service had a number of raters who scored independently and were blinded, another had two raters but only one blinded, and the other services had two blinded raters. A third rater, unaware of medical and clinical history and part of the GM Network, resolved disagreements for any case at any site. There were no scoring accuracy differences between the study sites, despite the differing processes.

#### Neurodevelopmental Outcome

Infants were followed to 12 -24 months post-term age. True positives were defined as a confirmed diagnosis of CP from a medical doctor. The diagnosis was typically given at a follow up time point by a developmental paediatrician or neonatologist based on neurological examination, clinical history, and developmental motor assessment. For infants not diagnosed with CP an abnormal outcome was defined as having scores on one

or more domains of the BSID-III (14) greater than 1 standard deviation below the mean at follow-up. If the only delay on the BSID-III was in the domain of language, the outcome was not coded as abnormal, given these children can go on to have a normal outcome despite delayed speech and language (16).

## Ethics

Ethics approval was obtained from all study sites, with The Royal Prince Alfred Hospital Human Research Ethics Committee as the lead committee and site specific approval from all other participating institutions. Parental consent was previously obtained from families at the point of GMA. The accompanying history data was abstracted from medical records.

## Statistical Analysis

This was a prospective study; with data analysis planned a priori to data collection. Study design and data analysis were reported in accordance with the STARD checklist for reporting of studies of diagnostic accuracy. Neurodevelopmental outcome data was compared with GMA results from the fidgety period. Statistical analysis was completed using SPSS using conventional sensitivity and specificity calculation methods. Confidence intervals were calculated for sensitivity and specificity for predicting an outcome of CP and for any abnormal outcome.

## Results

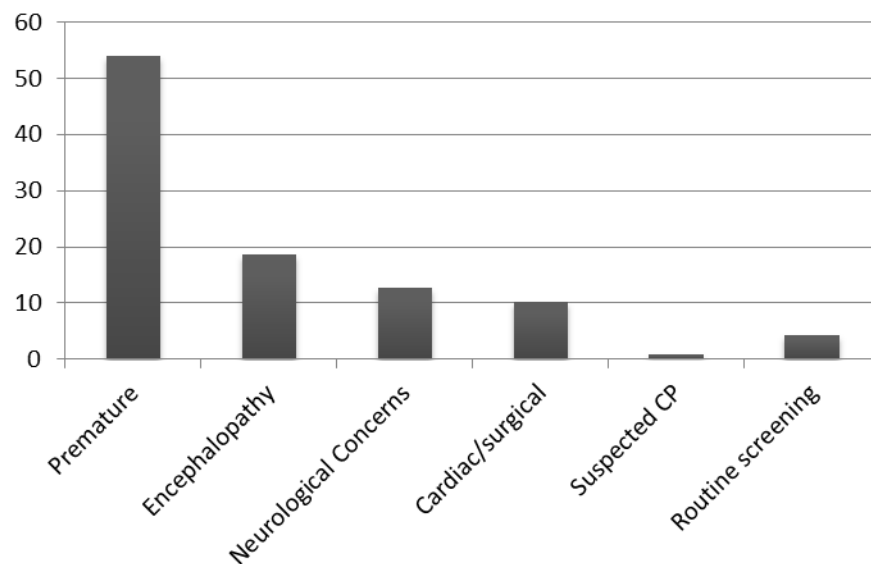
### Participants

Data were collected on all infants recruited and screened between 2011-2013, although some study sites did not collect data for the full study period while awaiting Ethics Clearance. Infants were all between 10-20 weeks post term age at the time of their GMA fidgety assessment and within 2 weeks of their first or second birthday at their one or two

year aged follow up. The most common reason for a GMA was prematurity followed by neonatal encephalopathy.

Complete one-year follow-up data were available for 187 infants. Partial data were available for another 72 infants who had not yet reached 12-24 months or were lost to follow up (n=62) and for n=10 whose GMA was not able to be scored. Reasons for conducting GMA are presented in Figure 1.

Figure 1: Reasons for conducting General Movements Assessment (%)



#### Quality of GMs

Data were analysed when both the fidgety GMA and 12-month outcomes were available, all other cases were treated as missing and excluded from the analysis. Of the 187 complete cases, n=138 were scored as normal fidgety (F+) i.e. low-risk for CP, n=48 were scored as absent fidgety (F-) i.e. high-risk of CP, and n=1 were scored abnormal fidgety (AF) i.e. high-risk for a neurological disorder. No adverse events were reported as a result of testing.

### *Neurological Outcome*

At one-year follow-up, of the n=187 cases: 102 children had a normal outcome and 40 children had a diagnosis of CP. A further 45 children had an abnormal outcome (not CP) (Table 1).

Table 1: GMA Fidgety Results and 12 Month Outcome Results

GMA result		12 month outcome		
Type of Fidgety		Normal	CP	Abnormal
<b>Normal</b>	n=138	n=99	n=1	n=38
<b>[F+]</b>	(74%)	(72%)	(<1%)	(28%)
<b>Abnormal</b>	n=1	n=0	n=0	n=1
<b>[AF]</b>	(<1%)	(0%)	(0%)	(100%)
<b>Absent</b>	n=48	n=3	n=39	n=6
<b>[F-]</b>	(26%)	(6%)	(81%)	(13%)

NB: Shading indicates the predicted outcome from GMA

First, in the n=138 with F+ movements there were n=99 with a normal outcome, n=1 later diagnosed with CP, and n=38 with a neurodevelopmental delay other than CP. Abnormal neurodevelopmental outcomes that were not CP included; n=1 with Prader-Willi syndrome, n=2 with hearing impairments and n=35 with global developmental delay, including n=1 suspected autism. The infants with global developmental delay ranged from mild motor and/or cognitive delay at 12 months to significant delays in both the cognitive and motor domains, as scored on the BSID-III.

Second, in the n=48 with F- movements, n=39 infants were diagnosed with CP by 12-18 months. Of the n=9 with F- and not diagnosed with CP all had a suspected or confirmed diagnosis of an abnormal outcome, including: n=1 had a genetic disorder; n=1 had a mitochondrial disorder; n=1 was recovering from meningitis; n=3 had moderate-severe global developmental delay; and n=3 had suspected CP at 12 months, but had not yet been formally diagnosed but were undergoing monitoring for a diagnosis of CP (coded as normal outcomes however at 12 months).

Third, the n=1 with AF movements had a motor delay at 12 months > 1 SD below the mean.

#### *Sensitivity and specificity*

Sensitivity and specificity scores were calculated for predicting CP and for predicting an abnormal outcome. Sensitivity for detecting CP was 98% (95%CI: 86.79-99.58) and specificity 94% (95%CI: 88.69-97.16). Sensitivity for detecting any abnormal outcome with abnormal or absent fidgety GMs was 54% (95%CI: 42.66-64.98) and specificity 97% (95%CI: 91.63-99.36).

The mean age of CP diagnosis for children identified at high risk of CP by the NSW GMA rater network was 8.5 months (SD=4 months). All infants identified as high risk of CP by F-GMs at 3-4 months were referred to early intervention services. The child later diagnosed with CP but with normal fidgety movements was also referred for early intervention due to concerns about motor development that were identified at follow-up from tests other than the GMA.

## **Discussion**

The GMA has consistently been shown to be a sensitive method for early detection of adverse neurodevelopmental outcomes especially CP. Although clinical use has generally been lacking outside the European context, this study confirmed that the GMA had excellent sensitivity and specificity to predict infants who would later be diagnosed with CP as well as those with normal outcomes. Our results are comparable to previous Australian and European studies demonstrating that the reliability of the GMA can be replicated in different parts of the world.

In the clinical setting, making a diagnosis of CP utilises a combination of robust, evidence-based tools including neuroimaging, neurological and standardised motor testing (2). The GMA is a highly predictive, non-invasive assessment that would be a valuable tool to add to the diagnostic work-up. Results of this study suggest that one benefit of early detection using GMA was that diagnosis occurred earlier, on average at 8.5-months compared to the Australian CP Register convention of 17-months. Previous Australian studies of preterm infants have followed infants until four years and demonstrated the value of the GMA in predicting adverse neurodevelopmental outcomes (15). The current study builds on this work with a broader group of high-risk infants, indicating very early identification of infants at the highest risk of motor impairment is possible and clinicians can be confident in referring those most in need of early intervention in the first few months of life. Clinical application of the GMA is useful to build a clinical profile of high-risk infants over time. It allows early entry of infants into targeted treatment programmes and enrolment into intervention studies during the period of greatest neuroplastic change.

All study infants designated “high risk of CP” on the basis of F- GMs were referred for early intervention. Unless there were very clear markers such as severe MRI findings, a definitive diagnosis was not given at this time, due to diagnostician-preferred practices (2). Importantly, our high sensitivity rates confirm that parents were not “worried unnecessarily”, given that almost all the infants with F- movements were found to have an abnormal outcome.

The high rate of abnormal outcomes found in this study is consistent with previous studies reporting outcomes in this high-risk population (18-20). We defined “abnormal” as a delay in at least one developmental domain of the BSID-III, which is the commonly used criteria in some follow-up services, although some services prefer to define an abnormal outcome as one where at least 2 domains of the BSID are  $> 1$  SD below the mean. In our analysis, only delays in language alone were not counted as abnormal due to the high level of variability in the emergence of these skills and high prevalence of early language delays that resolve (17). Not surprisingly, the GMA did not detect infants with developmental delay, highlighting the importance of using complementary assessments when following high-risk infants. Detecting a probable CP outcome versus one of mild developmental delay is important as it allows referral for diagnosis-specific intervention (21).

The GMA has now been embedded in clinical practice across NICU follow-up services in NSW, Australia. Use of the GM Rater Network has provided support for use of this tool and for the accuracy of results. To accommodate timing of peak fidgety period, a number of services have brought forward their initial follow-up clinic visit to 3 months of age rather than the conventional 4 months of age, in order to capture the GMs of at-risk infants during the ideal fidgety period.

It is recommended that the following high-risk groups of infants be screened using the GMA; preterm (including late preterm), all with neonatal encephalopathy, cardiac and surgical infants, those with stroke and neurological signs such as seizures, growth restriction and those with birth defects (22).

### **Limitations**

There are several limitations related to our study. First, as has been noted in previous publications sampling is a potential source of bias (23). All infants in this study were already considered at high risk of adverse neurodevelopmental outcome. Within our group the level of risk for CP specifically was variable. For example, the sample included term infants with HIE (very high risk for CP) and those with congenital heart defects, very preterm and late preterm infants. In addition, cases were recruited for the most part sequentially; however some cases were excluded as they were recruited to other studies, and some study sites did not collect data for the full study period owing to the differing timelines for study approval from Ethics.

Second, outcome data was mostly only at 12 months and it is known that milder forms of CP may only be diagnosed later in childhood when the diagnostician is sure that the motor impairment is permanent. Indeed  $n=3$  infants were suspected to have a mild CP due to tone abnormalities but had not yet been formally diagnosed but were being closely monitored by allied health practitioners who suspected they had CP. Potentially the rate of CP therefore has been under identified in this sample, and that the sensitivity of the GMA might have been even higher. Future studies should report 2-year outcomes in this high-risk cohort, as has been done previously in very preterm groups (15). Third, additional analysis of sensitivity and specificity of GMs in the earlier writhing period might



lead to the development of effective very early interventions that could be applied in the NICU within first 2-3 months of life closest to the timing of the brain injury. Fourth, sex of participants was deliberately not recorded so as to protect the anonymity of children with an absent fidgety score from small study sites, where the n-value was below the conventional  $n=4$  cut-off for anonymity. The accuracy of GMs is not however known to be affected by gender and therefore this is unlikely to have influenced the results. Finally, as previously outlined, the practice variation between sites in terms of number of blinded GMs scorers is a further limitation of the study.

## **Conclusion**

The GMA is an accurate, important and feasible assessment tool. It is non-invasive and therefore should be used regularly in the NICU environment and in follow-up programmes for early identification of infants at the highest risk of CP. It is clinically feasible to use and has excellent predictive validity when used by certified Australian assessors. Early detection of CP is possible and implementation of screening high-risk infants will allow those identified timely access to intervention services that aim to optimise their developmental outcomes. In conclusion, we recommend that the GMA be widely adopted into clinical practice, to close the know-do gap about late diagnosis of CP, which is potentially harmful to infants.

## **Acknowledgements**

The authors wish to acknowledge the assistance of Dr Karen Walker, Dr Ingrid Rieger and Ms Rosemary Day in data collection.

The authors declare no conflicts of interest. Ms Morgan is funded by an NHMRC doctoral scholarship.

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## Chapter 5 | Study 4 GAME (Goals-Activity-Motor Enrichment) PROTOCOL

### PUBLICATION

**Morgan C**, Novak I, Dale RC , Guzzetta A, Badawi N. GAME (Goals - Activity - Motor Enrichment): protocol of a single blind randomised controlled trial of motor training, parent education and environmental enrichment for infants at high risk of cerebral palsy. *BMC Neurology*. 2014; 14:(203).

Our systematic review (Study 2) revealed firstly the paucity of early intervention trials that accurately identified infants with CP in the first year of life, and secondly, that those interventions that were effective in this population were based on motor learning principles including enrichment of the learning environment.

We developed a novel early intervention programme we labelled GAME (Goals – Activity - Motor Enrichment) that focused on intensive motor training, co-delivered by therapists and parents in an enriched home environment.

This methods paper describes the GAME protocol for the randomised trials that followed (Studies 5 and 6).

### AUTHOR CONTRIBUTIONS

CM and IN have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and have been involved in drafting the manuscript.

NB, AG and RD have been involved in critically revising the manuscript for important intellectual content; and all authors have given final approval of the version to be published.

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**STUDY PROTOCOL**

**Open Access**

# GAME (Goals - Activity - Motor Enrichment): protocol of a single blind randomised controlled trial of motor training, parent education and environmental enrichment for infants at high risk of cerebral palsy

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## Abstract

**Background:** Cerebral palsy is the most common physical disability of childhood and early detection is possible using evidence based assessments. Systematic reviews indicate early intervention trials rarely demonstrate efficacy for improving motor outcomes but environmental enrichment interventions appear promising. This study is built on a previous pilot study and has been designed to assess the effectiveness of a goal - oriented motor training and enrichment intervention programme, "GAME", on the motor outcomes of infants at very high risk of cerebral palsy (CP) compared with standard community based care.

**Methods/design:** A two group, single blind randomised controlled trial (n = 30) will be conducted. Eligible infants are those diagnosed with CP or designated "at high risk of CP" on the basis of the General Movements Assessment and/or abnormal neuroimaging. A physiotherapist and occupational therapist will deliver home-based GAME intervention at least fortnightly until the infant's first birthday. The intervention aims to optimize motor function and engage parents in developmental activities aimed at enriching the home learning environment. Primary endpoint measures will be taken 16 weeks after intervention commences with the secondary endpoint at 12 months and 24 months corrected age. The primary outcome measure will be the Peabody Developmental Motor Scale second edition. Secondary outcomes measures include the Gross Motor Function Measure, Bayley Scales of Infant and Toddler Development, Affordances in the Home Environment for Motor Development – Infant Scale, and the Canadian Occupational Performance Measure. Parent well-being will be monitored using the Depression Anxiety and Stress Scale.

**Discussion:** This paper presents the background, design and intervention protocol of a randomised trial of a goal driven, motor learning approach with customised environmental interventions and parental education for young infants at high risk of cerebral palsy.

**Trial registration:** This trial is registered on the Australian New Zealand Clinical Trial register: ACTRN12611000572965.

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## Background

Cerebral palsy (CP) is the most common physical disability of childhood with a prevalence of 2.1/1000 live births [1]. Late diagnosis, conservative “wait and see” monitoring and late referral to early intervention is the prevailing norm for two main reasons. First, because only half of infants with CP have clearly identifiable risks in the newborn period, for example prematurity or neonatal encephalopathy (NE) [2], and second, because not all infants with prematurity or NE will go on to have CP. Wait and see monitoring can mean brain injured infants do not always receive intervention in the most crucial period of brain development [2]. Furthermore children with CP reach approximately 90% of their gross motor potential by age 5 (or younger for more severely impaired), but for 40% of this critical window the ultimate severity of their condition is largely unknown [3], however severity itself is a likely predictor of responsivity to early intervention. The field of neuroscience has repeatedly demonstrated the plasticity of the infant brain and persistence of neurogenesis and activity-dependent plasticity are two of the basic mechanisms at work [4]. Intervention for infants with brain injuries aims to optimise these neuroplastic mechanisms.

In recent years, research into the predictive validity of Prechtl's Qualitative Assessment of General Movements (GMs) has allowed earlier diagnosis of high risk of CP to be reliably made at 3 months of age [5,6]. GMs is now the gold standard tool for early diagnosis of CP because of higher specificity and sensitivity than other traditional tests such as neurological examinations, cranial ultrasound and MRI [7]. For the preterm population, the combination of GMs and evidence of white matter injury on MRI predicts CP at 3 months with 100% accuracy [6].

### Early intervention and early enrichment

Early intervention (EI) studies have typically not used this combination of assessment tools to recruit homogenous samples of infants at high risk of CP. Rather heterogeneous infants are included in EI studies and labelled “high risk” because they were preterm, display delayed development or had complex social issues [8]. In many of these studies the proportion of children who actually go on to be diagnosed with CP are relatively small resulting in underpowered type II trials for CP. As a result it is virtually impossible to ascertain the effects of EI on the motor outcomes of infants with CP. Most systematic reviews conclude that EI approaches currently in use for CP do not have any effect on motor outcomes greater than what would be expected as a result of maturation [9,10]. It is important to note, however, that evidence for the effectiveness of general EI to improve cognition is well established for the more heterogeneous “high risk” groups [11].

It remains to be determined whether intervention approaches that are goal-oriented and involve active motor

training [12,13] currently used in older children with CP are actually applicable to infants with a small emergent motor repertoire. In addition, what “active ingredients” from EI approaches are vital to maximise developmental outcomes?

Environmental enrichment (EE) has been proven to enhance neuroplasticity and promote memory and motor function in animal studies [14] but the effect in humans is less understood. In animal studies, an EE is defined as one that facilitates enhanced cognitive, motor and sensory stimulation. Although there is no agreed parameters for enrichment, these animal housing conditions typically include high levels of complexity and variability with arrangement of toys, platforms and tunnels being changed every few days to promote motor learning and memory. The motor opportunities afforded by EE are a critical success factor.

Translating these ideas into the human context is complex. Much more is known about the detrimental impact of deprivation (under-enrichment) on child development than is known about what constitutes enrichment for infants raised in “expected environments” [15]. Thus a continuum of enrichment is implied, but has not been well explained in terms of the type or amount of enrichment required for children who are not typically developing. One recent systematic review [8] has demonstrated a small positive effect on motor outcomes for infants at high risk of CP when the utilised interventions are based on principles of environmental enrichment. The enhanced plasticity mechanisms present in the infant brain allow it to be more strongly influenced by the environment than adult brains, so furthering our understanding of what constitutes enrichment for brain injured babies is important [16,17].

In children with CP the key environmental factors which influence motor development are yet to be determined, however clinical and neuroscience do provide a clear rationale for the urgent need for the development of EI programmes that focus on EE strategies to improve motor outcomes in these children [18]. Ulrich's [19] recent review discusses the opportunities for the development of early intervention programs which link neuroscience with clinical science and states in her summary, “A growing body of basic and clinical science results suggest we are missing the boat on opportunities for infants with motor disabilities if we do not develop more empirically based protocols to use very early in life in order to optimize developmental outcomes” [19], p10.

We have developed such a protocol, “GAME”, based upon the principles of motor learning and widely accepted EI frameworks including family centred practice [20] and the ecological framework [21]. Data from our recent pilot randomised controlled trial RCT (n = 13) indicates that GAME, a goal-oriented, intensive motor

training programme that actively involves parents and includes EE strategies, could be effective in advancing the motor trajectories of infants at high risk of CP [22]. After 12 weeks, GAME intervention infants ( $n = 6$ ) had an 8.05 point advantage on the Total Motor Quotient of the Peabody Developmental Motor Scales – second edition compared to infants who received standard care therapy ( $n = 7$ ). Although small, the pilot study confirmed feasibility of recruitment and randomisation procedures, and enabled confirmation of outcome measures and the sample size required for a larger RCT of GAME intervention. This proposed study will address this gap in the literature.

### Objective

The aim of this study is to evaluate whether a goal oriented, intensive motor training programme with EE strategies (GAME) is more effective than current standard care practices in influencing the early motor development of infants at high risk of CP.

### Methods

A single blind RCT with 2 parallel groups will be conducted to evaluate the efficacy of GAME compared to standard care. The outcomes of this trial are the infant's motor function after 16 weeks of intervention and at 12 and 24 months corrected age, home enrichment, parent perception of and satisfaction with their child's performance and parental well - being.

We hypothesise that:

1. Infants diagnosed with CP or at risk of CP that receive GAME intervention will have higher short term (after 16 weeks of intervention) Peabody Developmental Motor Scale (PDMS II) scores than infants that receive standard care
2. Infants diagnosed with CP or at risk of CP that receive GAME intervention will have higher long term (at 1 year of age) scores on the PDMS II scores than infants that receive standard care.
3. Infants diagnosed with CP or at risk of CP that receive GAME intervention will have higher Gross Motor Function Measure (GMFM) scores than infants that receive standard care at 1 year of age.
4. Infants who have received GAME intervention will have sustained higher PDMS –II scores long term (at 24 months) compared with infants who have received standard care.

### Study sample and recruitment

Thirty infants will be recruited from their treating institution, community physician or local therapist. The infants will be recruited in and around Sydney, NSW Australia. Seven NICUs and the Cerebral Palsy Alliance will actively recruiting to this study although infants

may be referred from any source. Study sites are listed in the Appendix.

All parents of eligible infants will be informed about the study only after they have had discussions with their medical team regarding the high risk status of their child, or a confirmed diagnosis of CP. Families will be given a site specific information sheet regarding the purpose and design of the study and have opportunity to speak with investigators before consenting to the study. Parents who do not wish to consent to the study will be offered standard community based therapy.

After consent is obtained, prior to randomisation, the investigators will visit the family at home to complete all baseline assessments and collect demographic and perinatal data. MRI and medical data will be obtained from the infant's medical record.

The Human Research and Ethics Committees of the Sydney Children's Hospital Network (SCHN), Cerebral Palsy Alliance (CPA) and the University of Notre Dame Australia (UNDA) have approved this study. The experimental design including time points and outcome measures are depicted in the CONSORT [23] flowchart (Figure 1).

### Inclusion criteria

Infants aged between 3 and 6 months (corrected age) with a diagnosis of CP or at high risk of CP are eligible for the study. Infants referred between 9–18 weeks post term age (PTA) will be screened using the General Movements Assessment (GMs). At least 2 certified assessors blinded to the infant's history will score the GMs videos. Infants with abnormal general movements (absent fidgety) are eligible for enrolment, ie 95% high risk of CP. Where assessors disagree, a third blinded assessor will be required to assess the video.

Infants over 18 weeks corrected age up to 6 months of age, outside the window of reliable GMs assessment, will be included on the basis of a confirmed CP diagnosis and/or abnormal neuroimaging as described by Krageloh-Mann [24].

Imaging commonly associated with CP include:

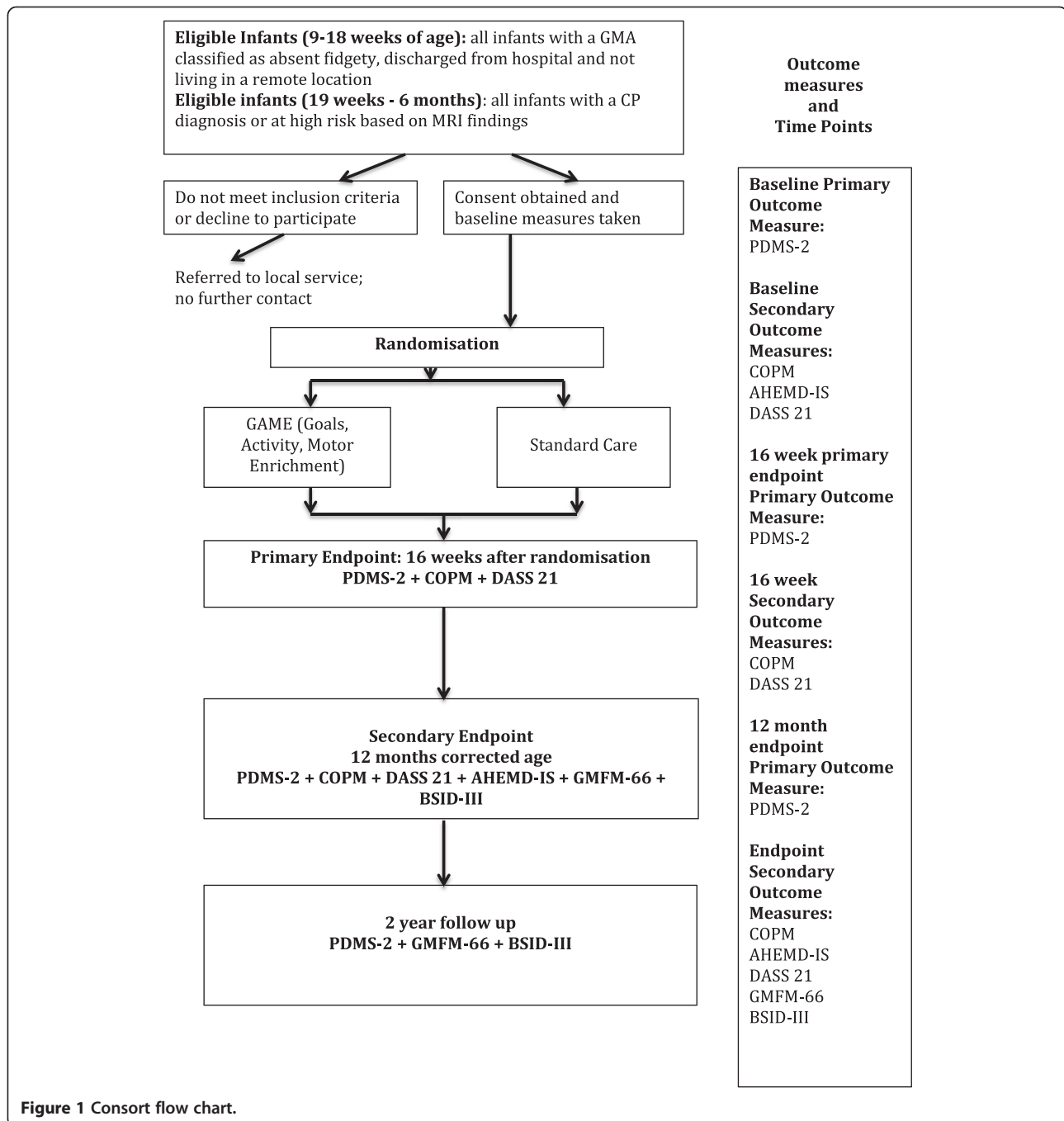
1. Periventricular Leucomalacia (PVL) and cystic PVL
2. Intracranial Haemorrhage
3. Periventricular infarction
4. Lesions of the basal ganglia and thalamus
5. Unilateral parenchymal injury eg middle cerebral artery infarction
6. Cortical malformation

A pediatric neurologist blinded to group allocation will confirm MRI features.

### Exclusion criteria

Infants otherwise eligible but with severe genetic abnormalities, or not discharged from hospital, or residing in





remote areas not accessible to the research team will not be eligible for the study.

#### Sample size

The planned study sample size ( $n = 30$ ; 15 per group) has been estimated from a power calculation based on our pilot data using motor composite scores of the PDMS-2, with an alpha value of 5% and power of 80%, using a minimal clinically important difference of 10%, accounting for a 20% dropout rate.

#### Randomization process

After informed consent and baseline measures are taken, an officer not connected with the study will randomise participants at a separate location using a pre-prepared random assignment schedule stored within 30 concealed opaque envelopes generated using computer generated random numbers. The Primary Investigator will be informed by the independent randomisation officer of group allocation and will inform parents. Twins will be randomised together due to the nature of the intervention.

### **Blinding arrangements**

The independent assessors will be blinded to group allocation and will carry out all assessments after randomisation. Assessments of the child's movement for the primary outcome measure and GMFM-66, will be completed via scoring from video. Other secondary outcome measure assessments will be conducted over the phone, via home visit or parent self report, as per the test and clinical conventions. Research Assistants from the Cerebral Palsy Alliance Research Institute and trained physiotherapists and/or occupational therapists will score the measures as the blind assessors.

It is not possible for either the participating families or those conducting the intervention to be blinded in this trial due to the nature of the intervention.

### **Intervention**

#### **Therapists**

Investigators CM, an experienced physiotherapist and IN, an experienced occupational therapist are the primary therapists providing the GAME intervention to maximise fidelity of the intervention. If a speech pathologist or family support worker is required based on identified family goals this will be provided. Infants in the standard care group will receive services from local therapists according to the centre's protocol. Typically in Sydney this would include physiotherapists and/or occupational therapists. Some sites offer a multidisciplinary team approach while others a keyworker model with a primary therapist.

#### **Interventions**

**GAME** is a therapy intervention based on contemporary motor theory. This intervention approach has been previously described in a small pilot RCT that tested the feasibility of GAME [22]. GAME intervention consists of three components: goal-oriented intensive motor training, parent education, and strategies to enrich the child's motor learning environment. Although described as distinct aspects of GAME, these components are fully integrated into therapy sessions with the emphasis on any particular component varying from session to session.

#### **Game part 1**

**Goal-oriented intensive motor training** Families collaborate with the therapists to determine a set of goals for their child's development [25]. Typically the goals would relate to motor development but might also include health related concerns known to affect development such as sleeping and feeding. The therapist plays an important role in helping parents set realistic and appropriately time framed goals. As goals are attained the family and therapist work together to develop new goals. These parent identified goal areas are targeted for

practice during therapy sessions and built into a home programme (HP).

The motor learning component of the intervention is based on the principles of motor learning and dynamic systems theory [26,27]. Therapist assessment of the relative contributions of weakness, selective motor control and altered tone to difficulties in goal achievement are discussed with the family and solutions are identified and tried [28]. Parents are encouraged to use their knowledge of their child's play preferences to elicit self-generated motor activity. Minimal manual guidance is provided when required and withdrawn as soon as the child has the idea of the movement or begins to demonstrate the ability to recruit a successful muscle action or sequence. Parents are coached in understanding "missing components" of the desired action and problem solve with the therapists ways of simplifying the task to enable at least part task attainment.

Motor tasks are scaffolded, so that the infant can always actively complete at least a part of the task [29]. As performance improves, the motor challenge is increased by altering the task or environment to encourage problem solving. Manual assistance is reduced or withdrawn as soon as the infant demonstrates self-initiated progress with the task; ensuring self-generated motor activity is promoted in all practice sessions. Once a motor skill is learned, variability of practice is introduced to increase the complexity and generalizability of the skill [30]. Early weightbearing and sit to stand from the parents' lap are routinely included for each infant even if standing is not identified as a specific goal. Rehabilitation research in older children and adults with brain injuries suggest that functional weight bearing exercises can both improve motor control and provide strength training [26]. Given that the expected impairments of CP include weakness and reduced selective motor control, early activation of muscles of the lower limb using both concentric and eccentric exercise could enhance the development of upright mobility. Similarly, practice of reaching and grasping a variety of objects is also a standard part of motor training for all infants in order to expose the infants who are expected to be delayed, to a variety of objects to advance grasp and reach behaviours [31]. Modified constraint induced movement therapy and/or bimanual training is used when asymmetrical hand function is evident.

Practice schedules are discussed and designed based on family time constraints. A written HP, illustrated with photographs and related to parent identified goals, weightbearing and reach and grasp is provided. The HP describes parenting strategies, environmental enrichments and child-activities as per published guidelines on effective home programmes [32]. Activities in the HP are organised into those in which the carer plays an active role and those where practice can be "set up" for the infant to carry-out independently. The HP is updated as goals are attained.

### Game part 2

**Parent education** Parent education is known to be an important component of early intervention that is grounded in family centred practice [33]. Since most of the infant's active practice opportunities are provided in the child's daily routines, parent education is vital [34]. In GAME intervention, parents are coached to identify their child's voluntary attempts to move and self-regulate, plus understand the usual trajectory of emergent motor skills and how to stimulate progress. Parents are trained in simple motor task analysis and coached in appropriate strategies to enhance their child's development both at a specific goal level and in general early learning and development principles. Parents are taught to optimise the best use of their infants' "awake" time and the naturally occurring opportunities for learning. Learning optimisation includes both parent-directed and structured practice of desired motor tasks, where the parent role is integral to the child's learning (e.g. creating repetitions) and constructing opportunities for independent play (e.g. playing alone with motor enriching toys set up for the child). Parents are encouraged to both observe the therapist eliciting a motor behaviour from the baby and to attempt it themselves. Specific feedback, in a warm and supportive context, is given to parents to enable them to tease out why some attempts were successful for the baby and others weren't. As new motor skills emerge parents are coached in strategies to increase the challenge of the task; for example removal of support or the introduction of more complex toys. The importance of allowing trial and error during practice is discussed and parents are encouraged to devise their own activities to enhance goal attainment. Prognostic information is given when possible as well as evidence based information regarding sleeping, feeding and responsive parenting.

### Game part 3

**Environmental enrichment** It is clear that many aspects of a child's environment influence his or her motor, cognitive and social-emotional outcomes. Parental responsiveness, a variety of daily experiences, equipment use and the structure of the physical space are all known to influence child development [35-37]. In GAME, all visits are conducted within the family's home and deliberate attention is paid to aspects of the home environment to enhance developmental outcomes. This enrichment includes assistance in setting up motor enriched play environments to promote child self-generated movements, exploration and task success. This includes instruction in careful toy selection "matched" to the desired motor task, plus physical set up of areas for practicing and repeating activities related to the identified goal areas, weightbearing, and reaching and grasping tasks. Conventional baby equipment (e.g. highchairs, toys) already purchased by the family is used wherever possible. The whole environment for

motor learning is taken into account and therefore intervention may also include: (a) evidence-based early learning stimulation and role modelling to enhance cognitive and language development (e.g. reading books to children, limiting passive television watching); (b) optimising sleep hygiene; and (c) feeding interventions (e.g. anti-reflux medications) to ensure adequate caloric nutrition and pain-free backdrops for learning. The importance of variable daily experiences for infants is deliberately addressed and support given when parents articulate difficulty leaving the house. Siblings and extended family members are also actively encouraged to take part in the HP and therapy sessions to promote: family knowledge; family acceptance; family wellbeing; repetition of learning opportunities; and provide a natural source of varied social interaction for the infant. Parent well-being is openly discussed and support given to parents to access appropriate services when required.

Home visits from the GAME treating therapists are offered weekly initially and then frequency of intervention negotiated with each family around their preferences, availability and family resources required to carry out the intervention with fidelity. Visits are approximately 60 to 90 minutes duration.

### Standard care

"Standard care" (SC) describes the current follow-up and/or therapeutic interventions used when an infant deemed at high risk of CP is discharged from hospital in New South Wales Australia. It is not possible to standardise the frequency, intensity or type of interventions received in the SC group. Approaches used are varied and might include neurodevelopmental therapy, the developmental skills approach, group therapy or motor learning approaches reflective of the current EI literature base. Most therapists include parent education on positioning and handling and suggested home activities within the therapy programme. In the pilot study, SC therapy was offered approximately monthly but ranged from fortnightly to 3 monthly. In order to monitor the mode, frequency and intensity of intervention received by those in the standard care group as compared to the GAME group, all parents will be asked to keep a "log book" so that these relevant parameters can be compared between the groups. Similarly since the actual interventions provided in SC are likely to vary between services, history taking will include information gathering regarding the type of interventions used.

### Outcome measures and procedures

#### *Peabody Developmental Motor Scales -Second edition (PDMS-2)*

The PDMS-2 [38] is the primary outcome measure in this trial and is a frequently used assessment of motor skills. This test is standardised and normed for children

aged from birth to 6 years and has been validated for use as a discriminative measure. Two studies have demonstrated that it is responsive to change in the CP population for both infants [39] and toddlers [40]. It has demonstrated concurrent validity with the GMFM [41] and the Bayley [42]. PDMS-2 assessments will be obtained at baseline, 16 weeks after therapy has commenced and at 12 months and 2 years. Assessments will be blind scored from video.

#### **Gross Motor Function Measure (GMFM)**

The GMFM [43] is a criterion-referenced tool that is widely accepted as the gold standard for gross motor assessment in children with CP. There are a total of 5 dimensions measured including rolling, sitting, creeping, standing and walking. Infants will be videoed during the assessment and blind raters will score from the video using the appropriate manual. The GMFM- 66 will be used in this study at the secondary endpoint, (12 months) and at the 2-year follow up.

#### **Canadian Occupational Performance Measure (COPM)**

The COPM [44] is an individualised criterion referenced measure of performance of a self-selected range of activities. Functional problem areas are identified, prioritised and rated for performance and satisfaction via a semi-structured interview. The COPM will be used to prioritise goals and measure change in performance and satisfaction. The COPM will be used at baseline, 16 weeks after therapy has commenced and at 12 months. Data will be collected via face to face or phone interview by independent raters.

#### **Affordances in the Home Environment for Motor Development-Infant Scale (AHEND-IS)**

The AHEND-IS [45] is a measure of the quality and quantity of motor enrichment opportunities available to a child within the home environment. This tool has demonstrated validity and reliability in the toddler format. Data is collected via a parent self report on a standardised questionnaire. A total raw score is calculated. This measure will be taken at baseline and at 12 months.

#### **Depression, Anxiety and Stress Scale-21 (DASS)**

The DASS-21 [46] is an adult self-report designed to measure the emotional states of depression, anxiety and stress. It is a 21-item questionnaire and will be used to measure parent emotional well-being at baseline, before randomisation and at all time points thereafter.

#### **Bayley Scales of Infant and Toddler Development Third Edition (BSID-III)**

The BSID-III [47] is a standardised and norm referenced assessment, which measures the cognitive, motor, language

and social-emotional development of infants and toddlers aged 0–3. It consists of a number of developmental play tasks that can be completed at the child's home and videoed for scoring by blind raters. Alternatively infants enrolled in follow up programmes from recruitment sites may be assessed by staff blinded to group allocation at their 1-year clinic appointment. Infants will be assessed on the BSID-III at 12 months and 2 years.

#### **Statistical methods**

Analysis will be conducted on an intention-to-treat basis using SPSS and reported according to the CONSORT statement. Descriptive statistics (frequencies, means and 95% CIs) will be used to describe the sample at baseline and data from each outcome measure used will be summarised for both treatment groups. Between-group differences following intervention will be analysed using multiple regression to determine whether group allocation predicts outcome. MRI classification, SES and comorbidities including vision impairment and epilepsy will be considered as covariates in the analysis.

#### **Discussion**

This paper outlines the design and background for a single blind RCT comparing a novel intervention "GAME" with standard care to improve the motor outcomes of infants at high risk of CP.

#### **Appendix Study Sites**

1. Cerebral Palsy Alliance, NSW Australia
2. Sydney Childrens Hospital Network, NSW Australia
3. Royal Prince Alfred Hospital, NSW Australia
4. Westmead Hospital, NSW Australia
5. Royal North Shore Hospital, NSW Australia
6. Liverpool Hospital, NSW Australia
7. Royal Women's Hospital, NSW Australia

#### **Abbreviations**

CP: Cerebral palsy; GMs: General movements; EI: Early intervention; EE: Environmental enrichment; GAME: Goals-Activity-Motor-Enrichment; HP: Home program; PDMS-II: Peabody Developmental Motor Scale -2<sup>nd</sup> Edition; GMFM: Gross Motor Function Measure; COPM: Canadian Occupational Performance Measure; BSID-III: Bayley Scales of Infant and Toddler Development- 3<sup>rd</sup> Edition; AHEND-IS: Affordances in the Home Environment for Motor Development – Infant version; DASS-21: Depression, Anxiety and Stress Scale – 21 version.

#### **Competing interests**

The authors report no declarations of interest, competing or financial. Ms Morgan is funded by an NHMRC/CP Foundation doctoral scholarship APP1018027 and is an employee of the Cerebral Palsy Alliance (CPA).

#### **Authors' contributions**

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. CM and IN have



made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and have been involved in drafting the manuscript. NB, AG and RD have been involved in critically revising the manuscript for important intellectual content; and all authors have given final approval of the version to be published; agree to be accountable for all aspects of the work.

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Received: 10 September 2014 Accepted: 2 October 2014

Published online: 07 October 2014

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doi:10.1186/s12883-014-0203-2

**Cite this article as:** Morgan *et al.*: **GAME (Goals - Activity - Motor Enrichment): protocol of a single blind randomised controlled trial of motor training, parent education and environmental enrichment for infants at high risk of cerebral palsy.** *BMC Neurology* 2014 **14**:203.

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## Chapter 6 | Study 5 PILOT STUDY

### PUBLICATION

**Morgan C**, Novak I, Dale RC, Badawi N. Optimising motor learning in infants at high risk of cerebral palsy: a pilot study. *BMC Pediatrics*. 2015; 15(1): 30.

This paper provides the results of a pilot study of the effectiveness of GAME intervention when compared to standard care. The pilot study tested both the feasibility of the processes involved in recruiting such young infants to a randomised trial, as well as the acceptability of GAME to parents. Importantly the 12-week pilot study allowed us to conduct a power analysis for the larger and longer planned RCT (study 6), and evaluate the suitability of our chosen outcome measures in this young population.

We found that the intervention was acceptable to parents and recruitment sources, with no study dropouts or adverse events occurring. The pilot study results demonstrated significant between-group differences in favour of GAME on one of the secondary measures – the Peabody Developmental Motor Scale. These findings enabled us to make minor adjustments to inclusion criteria and choice of measures for Study 6.

### AUTHOR CONTRIBUTIONS

CM and IN have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and have been involved in drafting the manuscript. NB and RD have been involved in critically revising the manuscript for important intellectual content; and all four authors have given final approval of the version to be published

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RESEARCH ARTICLE

Open Access

# Optimising motor learning in infants at high risk of cerebral palsy: a pilot study

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## Abstract

**Background:** The average age for the diagnosis of cerebral palsy (CP) is 19 months. Recent neuroplasticity literature suggests that intensive, task-specific intervention ought to commence as early as possible and in an enriched environment, during the critical period of neural development. Active motor interventions are effective in some populations, however the effects of active motor interventions on the motor outcomes of infants with CP have not been researched thoroughly, but pilot work is promising. The aim of this study was to determine the short-term effects of "GAME"; a new and novel goal-oriented activity-based, environmental enrichment therapy programme on the motor development of infants at high risk of CP and test study procedures for a randomized controlled trial (RCT).

**Methods:** Pragmatic 2-group pilot RCT to assess motor outcomes, goal attainment, parent well-being and home environment quality, after 12-weeks of GAME intervention versus standard care. GAME included: creation of movement environments to elicit motor behaviours; parent training in motor learning and task analysis; frequent practice of motor tasks using a programme that was individualised to the child, was varied and focused on self-initiated movement. Data were analyzed using multiple regression.

**Results:** Thirteen infants were consented, randomised, treated and completed the study. At study conclusion, the GAME group (n = 6) demonstrated an advantage in Total Motor Quotient of 8.05 points on the Peabody Developmental Motor Scale-2 (PDMS-2) compared to the standard care group (n = 7) (p < .001). No significant differences existed between groups on any other measure.

**Conclusions:** GAME appears to offer a promising and feasible new motor intervention for CP, with favourable short-term motor outcomes. A pressing need exists for an adequately powered RCT with long-term end points, to determine if GAME may advance these children's motor trajectory.

**Keywords:** Cerebral palsy, Infant, Environmental enrichment, Motor skill

## Background

Late diagnosis is the norm for children with cerebral palsy (CP) since very few diagnostic biomarkers exist; only half are unwell in the neonatal period [1]; and neuroimaging does not accurately predict severity except in severe cases. This most often leads to a "wait and see" approach, where brain injured babies are monitored but not referred for rehabilitation until marked developmental delay is evident. Formal diagnosis of CP is made on

average at 19 months and can be as late as 4 years for those mildly affected, usually after failed motor milestones, or the emergence of clinical signs such as spasticity or involuntary movements. Identifying infants at very high risk of CP early and discriminating them from those with other diagnoses could lead to the provision of more specific, timely and evidence-based CP rehabilitative therapies in the critical period of brain development [1]. Current thinking is that these diagnostic-specific interventions should be applied very early rather than delivering general early intervention (EI), in an effort to optimise outcomes and limit maladaptive plasticity [2,3].

A consequence of the lack of a definitive CP biomarker and late diagnosis is that only a handful of EI clinical trials

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exist where all participants actually have CP or are at very high risk of CP. Rather, most EI trials comprise of heterogeneous “at risk” populations, including many infants who go on to have normal outcomes, resulting in underpowered trials that do not tell us much about effect of EI in CP [4]. Studies specifically recruiting infants with brain injuries in the newborn period have typically not accurately identified infants who will later go on to be diagnosed with CP and disconcertingly, rarely have the study interventions resulted in motor improvements [5]. Prechtl’s qualitative assessment of general movements (GMs) is the most predictive assessment tool to detect infants, as young as 3 months who have the highest risk of CP, however it is rarely used when recruiting infants to intervention studies [6]. A further confounder in CP intervention studies is the heterogeneity of the condition, creating wide distributions of baseline and change scores making it difficult to detect change and identify best responders and non-responders.

As evidence of the benefits of Environmental Enrichment (referred to as EE from now on) on brain recovery grows [2,5], the focus of CP rehabilitation in older children has shifted towards approaches that emphasise goal-oriented activity-based therapy [7], and frequent task practice with deliberate creation of optimal environments for motor learning. These approaches, based on motor learning principles do not focus on passive interventions such as stretching, or the normalisation of movement like traditional Neurodevelopmental Therapy (NDT), but rather on task practicability and environmental context [8,9]. Improvements in motor behaviour depend upon intentional goal directed practice where the therapist is a “change agent” setting the stage for learning and facilitating the child’s exploration of effective movement solutions [10,11]. Examples of proven effective interventions utilising motor learning principles include constraint induced movement therapy and bimanual therapy. Typically these interventions are offered to children with CP from 2 years of age. Recently, a systematic review and meta-analysis of infants at high risk of CP, showed a small but significant effect of EE interventions on motor outcomes [5], suggesting that diagnostic-specific interventions including EE lead to better outcomes for infants. There remains a significant gap in our understanding of how the motor learning approaches effective in older children with CP can be applied to infants with a very limited motor repertoire. In addition, parent education is known to be an important component of early intervention [12] and since most of the infant’s active practice opportunities are provided within daily routines, parent education and coaching is crucial in order for the necessary practice to take place [13]. We therefore developed a new infant intervention approach: “Goals, Activity and Motor Enrichment” (GAME) that utilized motor learning

principles, goal-oriented activity-based therapy, parent education and EE strategies.

The aim of our study was to determine the short-term effects of GAME intervention on the motor development of 3–5 month old infants at very high risk of CP, and to test study procedures in preparation for a Randomised Controlled Trial (RCT). We hypothesized that infants in the GAME intervention group would have higher goal attainment and Peabody Developmental Motor Scale-2 (PDMS-2) scores after 12 weeks of intervention than infants receiving Standard Care (referred to as SC from now on).

## Methods

A pragmatic 2-group pilot RCT was used to explore the feasibility and effects of 12 weeks of GAME (Goals –Activity –Motor –Enrichment) intervention in infants at high risk of CP. GAME intervention is a home-based motor learning approach that aims to advance motor skills of infants and young children via motor task practice, parent education and environmental enrichment. The study also aimed to test the acceptability of randomisation procedures and the intervention to families and referring institutions, and to check outcome measure sensitivity and determine likely effect sizes.

## Study rationale

This study is both an RCT and a feasibility study [14]. We conducted and reported the pilot/feasibility study as an RCT because: 1) we wanted to test whether the randomisation procedure itself was acceptable to referring institutions and parents and therefore it was important to test whether or not it was feasible to recruit participants to an RCT. Since the GMs was new in our locality we were unsure that once the label “high risk of CP” was given to infants whether referral institutions were likely to promote a study where there was equal chance the infant would get a therapy program from a “CP specific” service vs general pediatric therapy programs, which are varied in type and intensity. Moreover, we wanted to see if parents “dropped out” of the study if they were randomised to SC; 2) The intervention was not previously described and we wanted to test the feasibility of both carrying out the intervention and its’ acceptability to parents; 3) The dearth of available outcome measures that are criterion-referenced for infants with disabilities is well established. As Goal Attainment Scaling (GAS) is widely used in toddlers and children with CP we wanted to test whether this was useful with infants who are yet to meet their motor potential; 4) We wanted to test statistical procedures. CP is a heterogeneous condition and the GMs assessment does not predict severity. We expected therefore to recruit infants across the severity

levels and for this reason used regression to enable us to account for differing motor ability affecting outcome.

### Participants

Thirteen infants were recruited from 6 Neonatal Intensive Care Units (NICUs) in the Sydney Children's Hospital Network (SCHN) and from the Cerebral Palsy Alliance, Australia. Infants 3–5 months of age were eligible for enrolment if parental consent was obtained and they had an abnormal GMs assessment score between 11–18 weeks post term age. Since “absent fidgety” GMs are the most predictive of a future diagnosis of CP, we used results from this period [6] rather than the earlier “writhing” period. GMs assessments were scored by at least 2 certified GMs assessors blinded to the infant's history. No official diagnosis by a medical professional was made at enrolment, rather, parents were counselled about the results of the GMs meaning their baby was at very high risk for CP. Infants were excluded if oxygen dependent, still an in-patient, or lived in a remote location precluding home visits from investigators.

### Procedures

Ethics approval was obtained from the University of Notre Dame Australia, Cerebral Palsy Alliance and the SCHN. After eligibility was determined, informed written consent was obtained and baseline measures taken. Infants were randomised to either the GAME or SC groups using sequentially numbered opaque sealed envelopes. The randomisation sequence was computer generated by an independent officer and group allocation was managed off-site. Intervention was carried out for 12 weeks as per the trial protocol for the 2-groups. Measures were taken at baseline within the child's home and were repeated at the primary end-point, after 12 weeks of intervention.

### Intervention

**GAME:** All GAME interventions were provided by the investigators (CM and IN) and carried out within the home environment. GAME has been described elsewhere [15] but always consisted of three components: goal oriented activity-based motor training, parent education, and strategies to enrich the child's learning environment.

1. Goal-oriented intensive motor training – parent identified goal areas were targeted for practice during the therapy session and after further assessment, a home program (HP), which was a detailed goal focussed activity based home practice plan was devised [16]. The therapist scaffolded all motor tasks, so that the infant could always actively complete at least a part of the task. As performance

improved, the challenge was increased by altering the task or environment to a new and appropriate level of difficulty. Manual assistance was provided by the therapist and parent only when necessary for safety or to give the infant the “idea” of the movement. Manual assistance was reduced or withdrawn as soon as the infant demonstrated self-initiated progress with the task; ensuring self-generated motor activity was the focus of all practice. Once a motor skill was learned, variability of practice was introduced to increase the complexity and generalizability of the skill. Early weightbearing and sit to stand from the parents' lap were part of each HP even if standing was not identified as a specific goal. Rehabilitation research in older children and adults with brain injuries suggest that functional weight bearing exercises can both improve motor control and provide strength training [17]. Given that the expected impairments of CP include weakness and reduced selective motor control, early activation of muscles of the lower limb using both concentric and eccentric exercise could enhance the development of upright mobility. Similarly, practice of reaching and grasping a variety of objects was a standard part of motor training for all infants in order to expose the infants who are expected to be delayed, to a variety of objects to advance grasp and reach behaviours [18].

The written HP was related to parent identified goals, weightbearing and reach and grasp. The HP included photographs, describing parenting strategies, environmental enrichments and child-activities as per published guidelines on effective home programmes [16]. Activities in the HP were organised into those in which the carer played an active role and those where practice could be “set up” for the infant to carry-out independently. The HP was updated once during the 12-week period.

2. Parent Education: Parents were coached to identify their child's voluntary attempts to move and self-regulate, plus understand the usual trajectory of emergent motor skills and how to stimulate progress. Parents were trained in simple motor task analysis and coached in appropriate strategies to enhance their child's development both at a specific goal level and in general early learning and development principles. Parents were taught to optimise the best use of their infants' awake time and the naturally occurring opportunities for learning. Learning optimisation included both parent-directed and structured practice of desired motor tasks, where the parent role was integral to the child's learning (e.g. creating repetitions) and constructing opportunities

for independent play (e.g. playing alone with motor enriching toys set up for the child). Parents were encouraged to both observe the therapist eliciting a motor behaviour from the baby and to attempt it themselves. Specific feedback was given to parents to enable them to tease out why some attempts were successful for the baby and others weren't. As new motor skills emerged parents were coached in strategies to increase the challenge of the task; for example remove support or introduce a more complex toy. The importance of allowing trial and error during practice was discussed and parents were encouraged to devise their own activities to enhance goal attainment.

3. **Environmental Enrichment** – Parents were encouraged and assisted to set up motor enriched play environments to promote child self-generated movements, exploration and task success. This included instruction in careful toy selection “matched” to the desired motor task, plus physical set up of areas for practicing and repeating activities related to the identified goal areas, weightbearing, and reaching and grasping tasks. Conventional baby equipment (e.g. highchairs, toys) already purchased by the family was used wherever possible. The whole environment for motor learning was taken into account and therefore intervention also included: (a) evidence-based early learning stimulation and role modelling to enhance cognitive and language development (e.g. reading books to children, limiting passive television watching); (b) optimising sleep hygiene, for example assisting with implementing sleep routines; and (c) feeding interventions (e.g. anti-reflux medications) to ensure adequate caloric nutrition and pain-free backdrops for learning. The importance of variable daily experiences for infants was deliberately addressed and support given when parents articulated difficulty leaving the house. Siblings and extended family members were also actively encouraged to take part in the HP and therapy sessions to promote: family knowledge; family acceptance; family wellbeing; repetition of learning opportunities; and provide a natural source of varied social interaction for the infant.

Intervention was customised for the child's motor ability, the family enrichment style, and parent goals. Therapist visits were weekly initially and then frequency was negotiated with each family around their preferences, availability and parental skill level to carry out GAME with fidelity. Visits typically lasted for 60 to 90 minutes.

**Standard Care:** Therapy intervention for infants at high risk of CP is available in New South Wales (NSW) free of charge, upon medical referral but varies enormously with no gold-standard guidelines in existence. Prior to study commencement, a survey was conducted amongst the study recruiting sites, revealing that the intensity of SC therapy was an average of 14-hours in the first year of life, spread typically over fortnightly or monthly appointments. Not all NICU recruitment sites offered ongoing intervention and referred infants to community-based organisations. The content of SC typically involved physical guidance to facilitate normal movement patterns and parental advice on positioning and handling. As no employer guidelines exist the choice of therapy approach is decided by the treating therapist and might have included NDT, motor learning, the developmental skills approach or a combination of approaches. For study purposes the SC offered to the control group was outside the investigators control both in terms of type of therapy and intensity of therapy, but was however representative of SC. Infants randomised to SC were referred to the provider by the centre referring the infants to the study. Infants received SC from either a hospital ( $n = 2$ ), a community-based health centre ( $n = 3$ ), or a Not-For-Profit Organisation ( $n = 2$ ).

#### Outcome measurement

The primary outcome measure was Goal Attainment Scaling (GAS), an individualised criterion-referenced measure of goal performance. Goals are set, with five possible outcomes specified for each goal. Composite T-scores are calculated for multiple goals and change over time is quantified using change scores and using conventional procedures recommended in literature [19]. We treated GAS scores as a continuous variable rather than ordinal although both approaches are used in the field and disagreement exists [19]. GAS is useful in CP rehabilitation for detecting incremental change in functional abilities that might not be detected on norm-referenced tools such as the Bayley Scales of Infant and Toddler Development [20]. GAS is widely used and recommended in childhood CP research because it is valid, reliable and responsive [19]. The use of GAS to measure outcomes in infants with CP has been validated [21] but never used in RCTs of infants under 12 months of age with limited motor repertoires and thus sensitivity is untested for this younger population. We therefore wanted to test the usefulness and applicability of GAS in very young infants across a broad spectrum of motor ability. We used GAS because we wanted to capture incremental change in performance. At the initial appointment after consent had been obtained, parent identified functional developmental goals for their child from interview. These were formulated into individual goal scales prior to the commencement of

therapy with the baseline level set by the investigators on the basis of an initial assessment of ability of the identified goal and confirmed by parent interview. GAS banks have been recommended in literature as a way of improving rigour. We used GAS banks wherever possible but individualised the goals as per the tool conventions when banks did not exist. For example, if the same baseline ability was evident for different participants for a specific goal the same GAS levels from a bank were used. As per test developer conventions parents were encouraged to identify 3 to a maximum of 5 goals for the 12-week period. Assessors were blinded to group allocation and scored the infant's 12-week GAS performance from video.

#### **Canadian Occupational Performance Measure (COPM)**

The COPM is an individualised, criterion referenced tool measuring perceived change in infant performance and parental satisfaction with performance over time on family priorities. The COPM is widely used in CP research and is valid, reliable and responsive [8,22]. During a semi-structured interview parents identified a number of areas that they would like to focus on with their baby during the study period. The standard 10-point scale was used to rate the infant's performance and their own satisfaction with the infant's performance on the identified focus areas. This was repeated after 12-weeks by a blinded assessor. An improvement of two or more points is regarded as clinically significant [22].

#### **Peabody Developmental Motor Scales - Second edition (PDMS-2)**

The PDMS-2 [23] is standardised norm-referenced tool, which is valid, reliable, and widely accepted. A total of 5 sub-scales are assessed including reflexes, locomotion, stationary, grasp and visual motor integration. A total motor quotient (TMQ) is calculated with a mean of 100 and SD of 15. Responsivity has been established for infants for the original version [24] and for toddlers with CP for the PDMS-2 [25]. The PDMS-2 was selected preferentially over the gold standard Gross Motor Function Measure (GMFM) because it evaluates fine motor skills that are targeted in many early intervention programmes.

#### **Home Observation Measurement of the Environment (HOME) - infant-toddler version**

The HOME [26-28] is a reliable, valid standardised measure of the quality and quantity of parent and home environmental stimulation and support available, scored from parent interview and direct observations. Sub-scales include parent responsivity, the availability of learning materials and variety of stimulation. The infant – toddler version is suitable for ages 0–3 [26]. Higher total HOME scores indicate a more enriched environment with 45 being the highest possible score.

#### **Depression, Anxiety and Stress Scale (DASS-21)**

The DASS-21 [29] is a mental health self-report measure of the emotional states of depression, anxiety and stress. The DASS-21 is psychometrically sound and is useful tool in the postnatal period for assessing psychological risks [29]. The primary caregiving parent completed the DASS 21 at baseline and study completion.

#### **Logbooks**

All families were asked to complete a logbook of the number and length of therapy sessions received over the 12-week study period. Families also documented the amount of time they spent carrying out therapist recommendations in the home environment. Parents who chose to access additional therapist-provided intervention documented the number of extra sessions.

#### **Statistical analysis**

Parent and infant characteristics and baseline measure mean scores were compared using independent t-tests, to ensure baseline equivalence of groups. Linear regression was used (where baseline scores were entered as covariates) to test the effect of providing GAME intervention compared to SC, on the infant's goal attainment and motor performance, the home environment and the parent's mental health. We chose to use linear regression over traditional t-tests as CP is known to be a heterogeneous condition and we expected to recruit infants across the severity spectrum leading to a wide variety of baseline scores and large standard deviations in both groups. Linear regression allowed us to treat baseline scores as a covariate. Severity could not reliably be imputed as a covariate in this short duration, small sample study, although this would be highly desirable, because 42% of infants change severity levels on the gold standard scale under 2-years of age [30]. Post-hoc analysis of the effect of total therapy dose (therapist delivered intervention plus parent delivered home program practice) in hours on the outcome was also conducted because there was insufficient power to use intensity of therapy as a covariate in the regression. Analyses were conducted on the basis of intention to treat. Missing values were imputed as last observation carried forward. Results were presented as between group differences with 95% confidence intervals.

Effect size was computed using Cohen's d. Commonly used criteria specify that a value below 0.2 is regarded as no effect, a value of 0.2–0.5 is a small effect, a value of 0.5–0.8 is a medium-sized effect and a value above 0.8 is a large effect [31].

#### **Results**

Thirteen infants from twelve families, mean age 17.6 weeks (SD =3.9), corrected for prematurity, and at very high risk of CP were recruited between September 2011 and



September 2012 (Table 1). Six infants were randomised to the GAME and seven to SC. Twins were randomised into the same group, as it would be impossible for parents to operationalize two different treatment approaches without intervention contamination. The flow of participants through the study is summarised in Figure 1. Adherence to study protocols was excellent with no dropouts. Participant characteristics are summarised in Table 1. Groups were equivalent at baseline on infant and parent characteristics. All child outcome data was normally distributed at both baseline and follow-up, therefore meeting the assumption for parametric statistics. The only exception to this was the HOME follow-up data, which was skewed right (kurtosis of 3.24) indicating ceiling effects on the measure.

#### Primary outcome at the primary end-point – GAS at 12 weeks

Primary and secondary outcomes are presented in Table 2. After 12-weeks of intervention, both groups improved.

The mean change score for GAME intervention was 38.67 (SD = 7.63) and 28.28 (SD = 18.33) for the SC group but with no statistically significant between-group differences and wide variation about the SC mean. Infants in both groups achieved the expected motor outcomes for parent-identified therapist-set goal scales (Table 2), improving 2 SDs from baseline on GAS T-Scores (GAS mean T-score = 50, SD = 10, with a T-Score 40–60 indicating achievement as expected). Parents usually identified 4–5 motor goals for their infants including rolling (77%), sitting (54%), reaching in prone (54%) and grasping toys (54%). One parent identified a non-motor goal (improved sleeping).

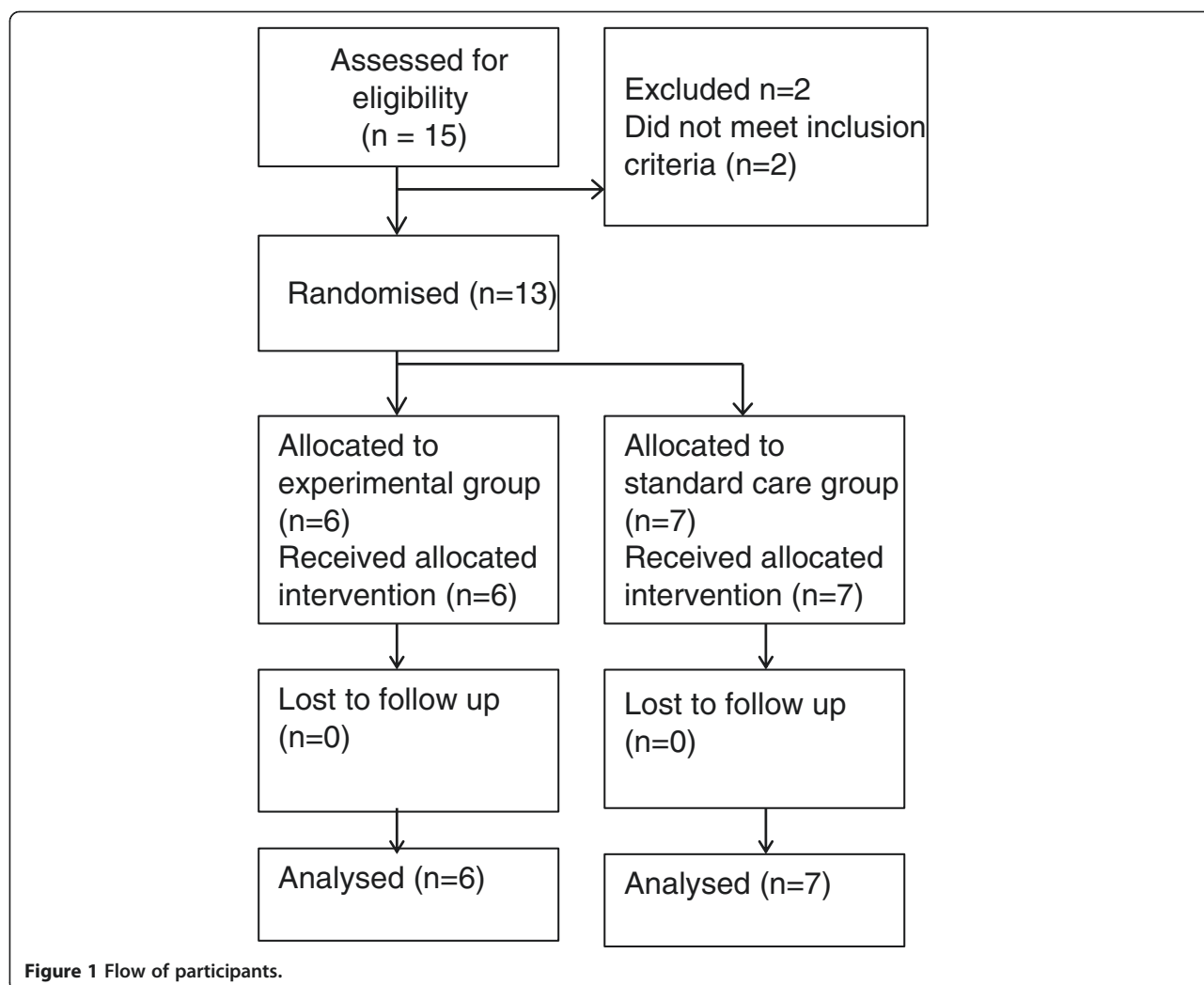
#### Secondary outcome measures

PDMS-2: After 12 weeks of intervention, the infant's motor abilities were assessed using the PDMS-2. Statistically significant between group differences were found in the Total Motor Quotient (TMQ) PDMS-2 scores, conferring an 8.05 point advantage to the GAME intervention

**Table 1 Baseline characteristics of participants**

Characteristic	GAME (n = 6)	Standard care (n = 7)	p value
Gestational age, mean (SD), weeks	35.50 (5.21)	33.57 (7.76)	0.61
Age at baseline, mean (SD), weeks (corrected for prematurity)	17.83 (4.17)	17.43 (3.95)	0.86
Sex: M/F	5/1	6/1	-
Birthweight, (kg)	2.85 (1.19)	2.40 (1.40)	0.54
Parent age, years			
Mother	33.00 (3.34)	33.43 (5.0)	0.86
Father	39.17 (5.12)	38.43 (2.64)	0.76
GAS T-score, mean (SD)	21.50 (1.22)	22.43 (0.96)	0.47
COPM Performance score, mean (SD)	3.03 (1.01)	3.19 (0.58)	0.42
COPM Satisfaction score, mean (SD)	4.26 (0.89)	4.81 (1.31)	0.36
PDMS-2			
Total Motor Quotient	80.17 (8.98)	81.29 (9.20)	0.83
Total Motor Standard Score, mean (SD)	35.67 (6.56)	36.43 (6.88)	0.87
HOME – IT score, mean (SD)	33.83 (3.66)	29.00 (8.08)	0.06
DASS 21 score, mean (SD)	19.67 (8.71)	24.57 (23.96)	0.16
Risk for CP*			
• Premature			
<28 weeks	n = 1/6	n = 3/7	-
>28 - < 37 weeks	n = 1/6	n = 0/7	-
• HIE	n = 2/6	n = 3/7	-
• Multiple Birth	n = 2/6	n = 0/7	-
• Hydrocephaly	n = 0/6	n = 1/7	-
Absent Fidgety General Movements Score (12–16 weeks PTA)	n = 6/6	n = 7/7	-
Diagnosis of CP between 5-12months	n = 4/6	n = 6/7	-

\*Primary risk factor - some participants had >1 risk factor. GAS = Goal Attainment Scaling; COPM = Canadian Occupational Performance Measure; PDMS-2 = Peabody Developmental Motor Scales – second edition; HOME = Home Observation Measurement of the Environment; DASS 21 = Depression, Anxiety, Stress Scales short (21 item) version; HIE = Hypoxic Ischaemic Encephalopathy; PTA = post term age.



group (95% CI 3.88-12.27;  $p < 0.001$ ). This represents just over 0.5 of a SD on the PDMS-2, which is probably clinically significant based on Wang's calculation for toddlers [25], but since no data on clinically meaningful change exists in infancy we cannot be certain. The total composite motor scores are also provided in Table 2 but the primary analysis was conducted on the TMQ because it is regarded as the most psychometrically robust estimation of motor ability.

We calculated sensitivity to change coefficients using Cohen's effect size, to assist with interpretation of the results. The Cohen's effect size for the GAME group was 0.5, which is considered a small to moderate effect size, while the SC group was -0.4, which Cohen defines as trivial since the change is  $< 0.2$ .

**COPM:** COPM performance and satisfaction scores improved in both groups with no between-group statistical differences.

**HOME:** Scores on the HOME improved in both groups however there were no statistically significant between group differences.

**DASS 21:** DASS 21 scores were calculated for 12 mothers and 1 father, with no between-group statistical differences found. Mean DASS 21 scores dropped in the GAME group by 13.67 points (SD = 11.83) but were stable in the SC group with an endpoint mean of 26.00 (SD = 28.75). The large SD in the SC group is explained by the scores of one parent who had a pre-existing severe mental health condition.

**Logbook:** Adherence to the GAME study protocol was high for all families. All GAME parents completed the logbook indicating HP and therapy time. All families in the SC group recorded therapy visits however 2/7 did not record HP time. These were the only missing values in the analysis and were coded as missing. Seven of the 13 infants were formally diagnosed with CP during the study period. Another 3 were formally diagnosed by 12 months and the developmental outcome of another 3 is unknown (2 in GAME group and 1 in SC). No information was collected about the type or severity levels of those diagnosed in this small pilot study.

**Table 2 Primary and secondary outcome measures with estimates of effect (between group differences and 95% confidence intervals)**

Outcome		Group		Estimate of effect (95% CI)	p-value
Time Point	Measure	GAME (n = 6)	SC (n = 7)		
		Mean (SD)	Mean (SD)		
Infant goal achievement on motor tasks:					
Baseline	GAS T-Score	21.50 (1.22)	22.43 (0.98)	-	-
12-weeks	GAS T-Score	60.17 (6.62)	50.71 (18.33)	7.37 (-12.71, 27.45)	0.43
Parent perception of infant motor performance-					
Baseline	COPM Performance	3.03 (1.01)	3.19 (0.58)	-	-
12-weeks	COPM Performance	7.24 (1.11)	6.58 (2.10)	0.72 (-1.49, 2.92)	0.49
Baseline	COPM Satisfaction	4.26 (0.89)	4.81 (1.31)	-	-
12-weeks	COPM Satisfaction	7.42 (1.05)	7.49 (2.56)	0.13 (-2.54, 2.79)	0.92
Parent enrichment style					
Baseline	HOME Score	33.83 (3.66)	29.00 (8.08)	-	-
12-weeks	HOME Score	39.83 (2.14)	36.43 (6.90)	-0.13 (-3.48, 3.22)	0.93
Infant motor development					
Baseline	PDMS-2 TMQ	80.17 (8.98)	81.29 (9.20)		
12-weeks	PDMS-2 TMQ	84.67 (10.21)	77.71 (8.85)	8.05 (3.88-12.23)	<0.00*
Baseline	PDMS-2 Total motor SS	35.67 (6.56)	36.43 (6.88)	-	-
12-weeks	PDMS-2 Total motor SS	38.83 (7.44)	33.86 (6.44)	5.72 (2.88, 8.56)	.001*
Parent well being					
Baseline	DASS 21 Total	19.67 (8.71)	24.57 (23.96)	-	-
12-weeks	DASS 21 Total	13.67(11.83)	26.00 (28.75)	-7.49 (-24.86, 9.89)	0.36

GAS = Goal Attainment Scaling; COPM = Canadian Occupational Performance Measure; PDMS-2 TMQ = Peabody Developmental Motor Scales – second edition Total Motor Quotient; PDMS-2 total motor SS = Peabody Developmental Motor Scales – second edition total motor standard score; HOME = Home Observation Measurement of the Environment; DASS 21 = Depression, Anxiety, Stress Scales short (21 item) version.

\*Indicates statistically significant.

Post-hoc analysis of the dose of therapy found a significant difference between groups in both the number of hours of therapy and the numbers of hours HP time. Infants in the GAME group received an average of 9.93 (range 7.5-15 hours) hours of therapy, which was almost three times higher than the 3.49 hours (range 1–6 hours) received by the SC group ( $p < 0.00$ ). Parents in the GAME group also spent more time carrying out the HP. The mean total dose of therapy (therapy plus HP) was 140.58 hours (SD 23.3) for GAME, and 54.17 hours (SD 32.62) for SC.

## Discussion

We hypothesised that GAME infants would have higher GAS scores than SC infants. Mean GAS score for the GAME group was a full GAS T-Score SD higher than that of the SC group. Statistical significance was not reached but this was not expected in this feasibility RCT which was underpowered to detect change, leading to a probable type II error. Interestingly goal achievement was higher and more homogenous in the GAME group whereas great variation was evident in SC scores, perhaps indicating GAME was more goal-focused - an issue

that could be further examined in future studies. We also noted that therapists found it difficult to predict the rate of infant's motor development at baseline given the limited motor repertoire at enrolment age and the lack of a robust severity measure for infants. Prior to intervention when goals were set, parents had difficulty predicting their baby's rate of development and their knowledge of what was "normal" varied. For example some parents did not know when a child would normally sit or walk. Parents were taught information in the parent education component of GAME but at baseline knowledge of milestone attainment affected levels of parental concern and GAS prediction accuracy. Although GAS has been shown to be an effective measure of motor change for infants [20,21] it might be more useful for documenting incremental change rather than standard milestone acquisition within clinical trials. We concluded that whilst GAS is sensitive in older children, the parent and therapist inaccuracy of predicting infant motor outcomes substantially affected sensitivity and therefore we would not recommend using GAS as a primary outcome in our own future GAME studies with infants.

Although this study was a small pilot randomised trial the secondary findings suggest that 12 weeks of GAME intervention might have a beneficial effect on the developmental motor outcomes of infants at high risk of CP. There have been no publications on the PDMS-2 about how much change is required in terms of motor quotients or raw score points to be regarded as clinically meaningful in this very young population. However, Wang et al. suggested a change of more than 9 raw score points on the PDMS-2 may be clinically significant [25] amongst toddlers. Our data exceeded the 9 points for all participants but was even greater for the GAME group, however this is a period of rapid motor development so greater change is expected, limiting interpretation of our results. While infants in both groups demonstrated improvements in terms of goal attainment, TMQ scores at 12 weeks on the PDMS-2 were significantly better in the GAME group. This difference could be the result of intensity alone or possibly a result of both the type and intensity of the intervention, as GAME parents engaged in more practice at home than did SC parents. Although the PDMS-2 motor gain is pleasing in this study, children with a permanent physical disability like CP usually fall further behind peers as developmental motor expectations increase. We would therefore expect that for a study of longer duration, the TMQ would drop in children with CP even if raw scores continued to increase. The small-moderate effect size we found in this pilot therefore needs to be confirmed in a larger sample of children over a longer period of time.

The lack of significant between-group differences on the subjective COPM was surprising given that the GAME groups scored better on the PDMS-2. This result might indicate that parents of infants at high risk of CP are pleased with any noticeable improvement or with natural developmental gains, and do not expect age appropriate performance or do not know what motor skills are considered “normal” at various time points. Most parents expressed a general goal for their child to “develop normally” although they were not sure what developmental milestones they should precisely expect. Even though the COPM and GAS scores did not demonstrate significant differences, we found the goal-oriented approach framed by these tools assisted parents to be more specific in identifying concerns, thus enabling focussed HP practice.

Environmental enrichment as measured by HOME scores demonstrated gains in both groups but there were no significant between-group differences. Notably ceiling effects existed, with 9/13 participants having higher than average baseline scores. Previous HOME studies have confirmed this ceiling effect [32]. It should be noted that the baseline HOME scores of the SC displayed a higher degree of variance than the GAME group due to 3

families with scores below the published mean of 31 (26) and only 1 in the GAME group. However after 12 weeks only one family in the SC group still scored below the mean. Future GAME studies should endeavour to explore the use of other measures of EE that might be more sensitive to change.

DASS 21 scores between groups were comparable at baseline and after intervention. At baseline, 23% of parents (all mothers) had abnormal depression scores but after intervention this had dropped to 15%. Miller et al [29] reported a DASS 21 depression rate of 19% in primiparous mothers, so our result was not surprising as mothers in the study experienced additional stressors in the newborn period. At baseline 31% of parents (all mothers) had symptoms of anxiety and this had reduced to 15% after 12 weeks of intervention. Our sample's baseline anxiety rate was higher than previously reported rate of 13% in new mothers. Premature birth and exposure to intense medical environments such as Neonatal Intensive Care Units are known risk factors for adverse psychological symptoms in mothers [33]. Adaptation to the diagnosis of CP is another known stress point and families participating our study were at risk of poor emotional health because of these factors. Evaluating parent wellbeing in studies of infants at high risk of CP is important as parental depression and anxiety can affect parent-infant attachment [33], negatively influence child cognition [34] and might impact the mother's ability to carry-out HPs.

### Feasibility of the trial

We found GAME was both feasible to carry out and acceptable to parents and referrers, with no dropouts, minimal missing data, and only  $n = 1$  parent declining to enrol. Ten of 12 families completed the logbook of HP and two forgot, but were able to estimate data. Although some described the logbook as tedious, it provided invaluable information about dose of practice.

GAME intervention fidelity was maintained as the same therapists provided intervention for each infant in the GAME group. Intensity of SC intervention was variable and little information was available about the type of SC intervention. Future studies should attempt to describe the content of SC more specifically.

The pilot study enabled us to confirm outcome measures for a planned larger RCT and calculate the sample size required with PDMS-2 as the primary outcome measure.

### Limitations

There were several limitations to this pilot study. First, the small sample size gives rise to the possibility that the absence of GAS, COPM and HOME differences could be type II errors arising from low statistical power.



Second, the study period was relatively short and infants were only 6–8 months old at the primary endpoint. It is therefore not clear whether the advantage observed in the GAME group would have been maintained long-term, particularly since at one-year of age the more demanding motor tasks of upright ambulation is the developmental norm. Third, as previously discussed, it is possible that the higher PDMS-2 GAME scores might have been solely attributable to the dose of therapy rather than GAME intervention. Dose of therapy will be entered as a covariate in the planned larger trial, however GAME intervention itself may in fact lead to greater parental participation in home practice as parent education is regarded as a key component of the intervention. Fourth, since SC is variable, areas of overlap in approach could well have existed creating contamination between the groups. Fifth, the lack of evaluator blinding across some measures may have unintentionally led to observer bias.

A larger blinded, RCT of infants from 3 months to one year is required to investigate whether the benefits of GAME confers a similar result to this pilot long-term. We did not find GAS the most appropriate primary measure to use in an RCT with young infants, and recommend a suite of measures including both a norm referenced tool complemented by criterion referenced measures capable of detecting incremental motor change, such as the COPM and GMFM. Future studies with larger sample sizes should also treat severity of motor impairment and dose as covariates in the analyses.

## Conclusions

This pragmatic pilot study compared 12 weeks of goal-oriented, activity-based, motor training centred on parent-elicited goals (“GAME”) to SC in infants at high risk of CP. While infants in both groups attained their goals, GAME infants had higher scores on a standardised assessment of motor ability, providing preliminary promising evidence of efficacy of GAME. Parent reported improvement in COPM performance and satisfaction and home enrichment scores improved in both groups. Mothers tended to report higher depression and anxiety scores than mothers without infants with a disability, indicating parental well-being is important to monitor. The recruitment processes and intervention was clinically feasible to do and acceptable to all families.

## Competing interests

The authors declare that they have no competing interests. The first author is supported by a doctoral scholarship co-funded by the National Health and Medical Research Council and the Cerebral Palsy Alliance Research Foundation. APP1018027.

## Authors' contributions

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. CM and IN have

made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and have been involved in drafting the manuscript. NB and RD have been involved in critically revising the manuscript for important intellectual content; and all 4 authors have given final approval of the version to be published; agree to be accountable for all aspects of the work. We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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## Acknowledgements

We thank the children and their families who participated in this pilot study and the SCHN for assistance with recruitment. We acknowledge and sincerely thank Jane Berry, Monique Hines, Petra Karlsson and Richard Barclay for their assistance with blind scoring of infant and family assessments.

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Received: 6 September 2014 Accepted: 13 March 2015

Published online: 01 April 2015

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## Chapter 7 | Study 6 GAME RCT

PUBLICATION (*submitted format*)

**Morgan C**, Novak I, Dale RC, Guzzetta A, Badawi N. Phase 2 single blind randomised controlled trial of GAME (Goals - Activity - Motor Enrichment) in infants at high risk of cerebral palsy. *Submitted*.

The final study followed on from the pilot (Study 5) and recruited 30 infants at high risk of CP or with a diagnosis of CP. We used the Peabody Developmental Scales as the primary outcome measure. Since the infants were between 3 and 6 months at enrolment, we collected data after all infants had received the same number of weeks of intervention (16 weeks) and then again when all infants were the same age (12 months corrected age).

At 12 months the infants were additionally assessed with both a norm-referenced developmental assessment (Bayley Scales of Infant and Toddler Development) and criterion referenced Gross Motor Function Measure. Infants in GAME had superior motor scores on all assessments when severity of injury was taken into account.

This study provides new and much needed evidence that rehabilitation intervention based on the principles of motor learning and environmental enrichment can advance the motor skills of infants with CP.

### AUTHOR CONTRIBUTIONS

CM and IN have made substantial contributions to conception and design and acquisition of data.

CM conducted data analysis and interpretation of data and drafted the manuscript. RD blind scored neuroimaging and AG assisted with blind scoring general movements assessments. IN, NB, RD and AG have been involved in critically revising the manuscript for important intellectual content; and all 5 authors have given final approval of the version to be published

NOTE: *This paper has been submitted for peer review to **Neurorehabilitation and Neural Repair**.*

## **Phase 2 single blind randomised controlled trial of GAME (Goals - Activity - Motor Enrichment) in infants at high risk of cerebral palsy**

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**Funding Source:** Ms Morgan is personally supported by an NHMRC/Cerebral Palsy Foundation Doctoral Scholarship 1018027.

**Financial Disclosure:** The authors have no financial relationships relevant to this article to disclose.

**Conflict of Interest:** The authors have no conflicts of interest to disclose.

WORD COUNT: 4112

TABLES & FIGURES: total 4

## **ABSTRACT**

**BACKGROUND:** Cerebral palsy (CP) is caused by a lesion in the developing infant brain. Recent neuroplasticity literature suggests that intensive, task-specific intervention ought to commence as early as possible during the critical period of neural development.

**OBJECTIVE:** To determine whether “GAME”, a motor learning, environmental enrichment intervention, is effective for improving motor skills in infants at high risk of CP.

**METHOD:** Single blind randomised controlled trial of GAME versus standard care. Primary outcome was motor skills on the Peabody Developmental Motor Scales-2 (PDMS-2). Secondary outcomes included Canadian Occupational Performance Measure (COPM), Bayley Scales of Infant and Toddler Development (BSID-III) and Gross Motor Function Measure-66 (GMFM-66). Outcome assessors were masked to group allocation and data analyzed with multiple regression.

**RESULTS:** Of n=30 3-6 month old infants enrolled, all received the assigned intervention until 16 weeks post enrolment. At 12 months of age, n=26 completed assessments. At both time points there were significant between group differences in raw scores on the PDMS-2 in favour of GAME ( $p < .03$ ) and at 12 months on the total motor quotient ( $p < .05$ ). Significant between group differences also favored GAME participants in the composite scores of the cognitive and motor scales of the BSID-3 and satisfaction scores on the COPM at 12 months.

**CONCLUSION:** GAME intervention appears to result in advanced motor and cognitive outcomes when compared with standard care. Further research is needed to evaluate whether these gains have any impact on severity of CP in the long term.

### **Trial registration**

This trial is registered on the Australian New Zealand Clinical Trial register: ACTRN12611000572965

## Introduction

Cerebral palsy (CP), the most common physical disability of childhood, occurs because of a lesion in the developing brain<sup>1</sup>. The lesions associated with an eventual diagnosis of CP usually occur during the prenatal or perinatal period. A small percentage acquires their injury after the neonatal period and account for approximately 5.6% of CP<sup>2</sup>. Since the brain injury of CP occurs early it is important to develop evidence based rehabilitation protocols that enhance the neuroplasticity mechanisms at work in the developing brain<sup>3</sup>. Many effective rehabilitation interventions for older children with CP exist<sup>4</sup>, but most have not been trialled early with infants because recruitment is difficult, since the diagnosis typically occurs after 18 months of age. Consequently although early intervention is endorsed for high-risk infants, the efficacy for infants with CP is not yet firmly established<sup>5</sup>. Early intervention research in the form of clinical trials for infants is burgeoning<sup>6-8</sup> with new knowledge expected in the coming years.

We developed an early intervention programme, GAME (Goals Activity Motor Enrichment)<sup>9</sup> that was first tested in a small pilot study (n=13)<sup>10</sup> with promising results in improving motor outcomes of GAME participants when compared to standard care. Our earlier pilot also established feasibility of procedures for recruitment and randomisation. The aim of this phase 2 study was to determine whether GAME intervention improved motor outcomes and parent perception and satisfaction with motor performance after 16 weeks of intervention, and at

12 months when compared with SC. We hypothesized that infants randomised to GAME would have superior motor skills at both time points.

## **METHODS**

### **Participants**

Infants were included if they were corrected age 3-4 months and: scored as “absent fidgety” on General Movements Assessment (GMA); OR were aged 5-6 months with a CP diagnosis OR had abnormal neuroimaging such that a CP diagnosis was considered extremely likely. Infants were excluded if they were inpatients, had medical conditions that precluded active involvement in therapy or lived in a remote location not accessible for home visits by the research team.

### **Study timeline and protocol**

Infants were recruited from 6 participating Sydney hospitals with Neonatal Intensive Care Units (NICUs) and the Cerebral Palsy Alliance between February 2013 and June 2014. The study received ethical approval by the Sydney Children’s Hospital Network, the University of Notre Dame Australia and the Cerebral Palsy Alliance human research ethics committees. Once eligibility was determined, parental consent was obtained and all baseline assessments and demographic data were collected.

Motor severity is a known predictor of responsiveness to intervention. Due to the young age of the participants, the Gross Motor Function Classification Scale (GMFCS) could not to be used to reliably rate the severity of motor impairment<sup>11</sup>. We therefore needed to use the best clinically available severity predictor which is neuroimaging blind-scored by a paediatric neurologist and paediatric radiologist to estimate severity of the brain injury. Neuroimaging was

not available for n=2 and only cranial ultrasound was available for n=3. A score form was created from best available literature<sup>12-14</sup>. When multiple images were available, the series closest to term equivalent age was used for preterm infants and closest to day 7 for infants with hypoxic ischaemic encephalopathy.

Severity results were ordinally coded as: 0 = normal OR unlikely to have CP; 1=likely to have ambulant CP (e.g. focal vascular insults); and 2= likely to have non-ambulant CP, (e.g. significant basal ganglia/thalamus lesions or diffuse brain injury). When neuroimaging data was not available it was coded as “missing”.

An officer not connected with the study randomised participants at a separate location. The Primary Investigator was informed of group allocation and then informed parents. The allocation sequence was computer generated and assignments concealed using sequentially numbered opaque envelopes. No stratification was used in terms of gestational age, or type or severity of brain injury.

## **Intervention**

Infants randomised to standard care either continued with pre-existing therapy arrangements or were referred to a local intervention site by their referring institution. Appendix 2 contains a checklist of intervention content for both GAME and standard care as recommended by the Tidier Guidelines<sup>15</sup>.

### *GAME Intervention*

GAME is an acronym for Goals, Activity and Motor Enrichment. The intervention is based on the principles of active motor learning, family centred care, parent coaching and environmental enrichment. Refer to Appendix 2 for a detailed



description. The intervention was offered at least fortnightly until the infants first birthday (corrected age).

### *Standard Care Intervention*

“Standard care” (SC) describes the current follow-up and/or therapeutic interventions used when an infant at high risk of CP is discharged from hospital. It is not possible to standardise the frequency, intensity or type of interventions received in the SC group. Therapeutic approaches used and modes and intensity of delivery are varied. Appendix 2 contains information about SC in this study.

### **Outcome Measures**

The primary outcome was motor skills as measured by the Peabody Developmental Motor Scales -Second edition (PDMS-2), a norm referenced assessment of gross and fine motor skills in children 0-6 years. Results are expressed as raw scores, standard scores and total motor quotient (TMQ), which is regarded as the best estimator of motor ability. The PDMS-2 has been validated as a discriminative measure and two studies have demonstrated its’ responsivity to change in infants and toddlers with CP<sup>16-17</sup>. PDMS-2 assessments were obtained at baseline, 16 weeks after therapy had commenced and at 12 months corrected age. Two highly experienced assessors (one physiotherapist and one occupational therapist) who were blinded to group allocation scored the PDMS-2 assessments from video. High inter-rater reliability has previously been established for this tool<sup>18</sup>.

Secondary outcomes included the Canadian Occupational Performance Measure (COPM)<sup>19</sup>, an individualised criterion-referenced measure of performance and satisfaction with performance of a parent-selected range of

activities. The COPM was used at baseline to prioritise parent goals for their baby's development and assess parent's perception of their infants' performance on identified goals and their own satisfaction with the infants' current ability. After 16 weeks of intervention the COPM was rescored and new priority areas identified. At 12 months the second COPM was rescored. Two blinded assessors scored all COPMs post enrolment via telephone call.

Motor and cognitive skills were assessed using the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) and motor function using the Gross Motor Function Measure (GMFM-66)<sup>20</sup>. These measures were taken at 12 months only and scored by blinded assessors.

Enrichment of the home environment was assessed with the Affordances in the Home Environment for Motor Development – Infant Scale (AHEMD-IS)<sup>21</sup>.

AHEMD-IS identifies opportunities available within the home to promote motor development, including characteristics of the indoor and outdoor environment and the presence of a range of toys and equipment. This tool is a validated, parent self report however sensitivity to change has not been established<sup>22</sup>.

Total score possible for infants younger than 11 months is 66 while from 12 months possible total score is 93, to account for the expected increase in available learning materials. To compare change from baseline to follow-up at 12 months we compared percentages of total score, as per test developer recommendations (personal communication).

The Depression, Anxiety and Stress Scales – 21 (DASS-21)<sup>23</sup> is an adult self-report designed to measure the emotional states of depression, anxiety and stress. It is a 21-item questionnaire and was used to measure parent mental health at baseline, 16 weeks after randomization and at the 12-month time

point. Lower scores are associated with more normal levels of depression, stress and anxiety.

### *Sample size estimation*

The study sample size was estimated from a power calculation based on our earlier published pilot data using motor composite scores of the PDMS-2. We considered a clinical meaningful difference between the groups to be at least 5 standard score points (0.5 of a standard deviation). With an alpha value of 5% and power of 80%, using a minimal clinically important difference of 10% and accounting for a 20% dropout rate, we estimated the sample size required to be  $n=30$ ; 15 per group.

### *Statistical Analysis*

Analysis was carried out using SPSS and reported according to the CONSORT statement. Descriptive statistics (frequencies, means and 95% CIs) were used to describe the sample at baseline. Random missing data was imputed as last observation carried forward. Where there were no results available due to dropouts, only the data available were analysed so as not to introduce new biases. Between-group differences for child outcomes were analysed using multiple regression to determine whether group allocation predicted outcome. As infants were too young to accurately use GMFCS as a motor severity variable, a blunt neuroimaging +/- vision impairment severity variable was used as a covariate within the regression analysis. The severity variable was the aforementioned imaging ordinal score, plus a weighting point of +1 if the infant had severe vision impairment (i.e. consistently visually unresponsive to a moving toy stimulus; but motorically responsive to the same stimulus if an

auditory cue was paired to the stimulus), since vision impairment is a known confounder of motor development. Outcomes on the COPM were analysed using linear regression without the severity covariate. Parent mental health scores and home environment scores were compared with independent t-tests.

## **RESULTS**

Thirty infants from twenty-nine families were recruited between February 2013 and June 2014 and randomised to GAME (n=15) or SC (n=15). Mean age at enrolment was 17.9 weeks (SD 5.31). There was one set of twins randomised to SC and two infants who were twins randomised to GAME. The flow of participants is summarised in Figure 1. Adherence to study protocols was excellent until the 16-week time point with no dropouts and all participants receiving intervention as per protocol.

Between the 16-week primary endpoint and 12 month follow-up, 4 infants dropped out of the study, all from GAME group. Reasons for drop out included: relocation overseas or interstate for increased family support (n=3 of 4) and experimental stem cell treatment (n= 1 of 4). Data was analysed for all infants remaining in the study at 12 months, n=11 in GAME and n=15 in SC. In the 12-month analysis, missing data could not have substantially biased the secondary results because there was only after treatment BSID-III and GMFM-66 data, plus baseline and severity covariates were available for all individuals and included in all analyses<sup>24</sup>.

Participant characteristics are summarised in Table 1. Groups were equivalent at baseline on infant characteristics, except for age at enrolment where the

GAME infants were about 4 weeks younger by chance. Social risk was classified as “high” or “low” based on previously used criteria<sup>25</sup>. There were no significant between group differences on child motor function (table 2) at baseline. Parent mental health scores were different at baseline with GAME parents having higher rates of depression, but no between group differences on the other sub-scales or total score.

### **Child Outcomes**

Primary and secondary outcomes for GAME and SC infants are presented in table 2.

#### *Primary Outcome 16 weeks after enrolment*

After 16 weeks of intervention, no statistically significant between group differences were found on the TMQ but GAME participants were 0.5 of a SD better off. Significant between group differences were found in change in raw scores in favour of GAME.

#### *Primary outcome 12 months corrected age*

Statistically significant between-group differences were found at 12 months on both the PDMS-2 TMQ and raw scores favouring GAME. Confirmatory, significant between-group differences were evident on the other motor measures, the GMFM-66, BSID-III composite motor scores ( $B = 15.23$ ; 95% CI 1.21, 29.25;  $p < .04$ ), and BSID-III fine motor standard scores alone, all favouring GAME. No significant differences existed for the BSID-III gross motor scale alone. In addition, mean BSID-III cognition scores were significantly higher for GAME at 12 months.

COPM

After 16 weeks of intervention both groups showed clinically meaningful change on the performance scale of the COPM. Significant between group differences were found in favour of GAME; mean change 3.55 (1.92) compared to 2.58 (2.21) for SC. There were no statistically significant differences between the groups in change scores on the satisfaction scale (GAME: 1.62 [SD 3.22] and SC: 2.00 [SD 1.78]).

At 12 months parent perception of their infant's movement skills did not significantly differ between the groups, despite only the GAME groups' COPM improvements reaching clinically significant thresholds of >2 points (performance change scores: GAME 2.57 [2.44]; and SC 1.09 [1.06]). Parents of infants in GAME did however have higher rates of satisfaction with their child's improvements (satisfaction change scores: GAME 2.66 [2.68] and SC 0.39 [1.17]).

#### *Child Diagnostic Outcomes*

Appendix 1 contains diagnostic outcome data for all 30 infants. At 12 months of age n=25 (83%) had received a diagnosis of CP including 3 of the 4 who had dropped out of the study. A further two infants were globally delayed, two were undiagnosed but displaying neurological abnormalities such as motor asymmetry and the developmental outcome of one infant was unknown. Of the 3 children with either no imaging or normal imaging, n=2 had mild diplegia and n=1 had monoplegia and cognitive delay at 12 months.

#### *Parent and environment outcomes*

Between-group differences on the AHEMD-IS scores at 12 months were non significant. DASS 21 scores were compared at 12 months and no statistically significant differences existed between the groups in total DASS 21 score or in any of the subscales (Table 3). Mean values for both groups dropped to more normal values between the 16-week time point and 12 months.

#### *Dose of intervention*

Complete logbooks were kept by 10 GAME families and 7 SC families and were collected at 12 months. Hours of face- to-face therapy could be ascertained for all families, however total dose could only be calculated for those with completed logbooks. Infants in GAME received a mean of 21.91 (SD 4.25) hours of therapy (median 22 hours) over the study period and SC 14.82 (SD 12.89) hours (median 13 hours). Parents in GAME reported they spent a mean of 47.70 (23.30) minutes per day (median 54 mins) carrying out the home programme while SC parents spent 42.29 (35.87) minutes (median 30 mins). The total dose of therapy for GAME infants from enrolment until 12 months was 216.00 (87.26) hours and for SC infants 164.29 (98.79) hours. There were no statistically significant differences in dose of therapy over the entire study period ( $p = .27$ ), however there was a trend towards more intensive face-to-face intervention for GAME participants ( $p = .09$ ).

## **DISCUSSION**

GAME intervention appears to lead to improved short and medium term motor outcomes when compared with a similar dose of SC. This is evidenced both in the norm referenced measures (PDMS-2 and BSID-III) as well as the criterion referenced GMFM-66. GAME appears to offer a new and positive benefit to

developing the motor skills of infants with CP, which is the first clinical trial data in CP to suggest this, since Palmer's seminal work in the 1980s.

The PDMS-2 TMQ scores were not statistically significant after 16 weeks, despite an estimate of effect of 7.5 favouring GAME, probably with the effect washed out due to large variances in both groups. At baseline, the TMQ variance was 0.5 of a SD for both groups, but increased to >1.0 SD by 16-weeks, indicating: (a) infants were of heterogeneous severities with varying capacities to respond to intervention; and (b) that norm referenced assessments might overestimate ability at younger ages, when infants have a more limited motor repertoire. At baseline, mean PDMS-2 TMQ scores for both groups were "below average", but after 16 weeks had dropped further into the "poor" range for both groups, despite receiving intervention. At 12 months the TMQ had dropped further again, into the "very poor" range for SC participants. This finding was not unexpected. Infants with CP continue to develop and "gain" raw score points over time, but are not expected to perform within the "normal range" but rather fall further behind peers over time. GAME appeared protective, that is, GAME participants did not fall as far behind.

The great majority of our sample had bilateral brain injuries albeit of varying severities, whereas in the CP population one third typically have unilateral injuries with milder motor disabilities<sup>26</sup>. In addition during the study period it became clear that 8 of 30 (27%) had severe vision impairments (4 per group), which exceeds the CP population norm of 10%<sup>2</sup>. Vision impairment is a known contributor to delayed motor development<sup>27</sup> and in children with CP is a predictor of non-ambulation<sup>28</sup>. These sampling errors meant that our study sample was "more severely affected" than a representative CP "population



sample". In practice this may have meant our recruited sample might have been lower responders than a more representative CP population sample.

Given the unexpectedly high number of infants with severe vision impairments that were recruited to this study we would recommend formal visual function assessments be completed early (at around 3 months) <sup>29</sup> to allow appropriate supports and intervention to be put in place.

After intervention, cognitive scores as measured by the BSID-III were superior for GAME infants, which we hypothesise could be a result of the environmental enrichment component built into GAME intervention. A recent meta-analysis demonstrated that in vulnerable families home visiting had a small positive mean effect on child cognitive outcomes<sup>30</sup>. The consistency of home visiting in GAME allowed specific exchanges and information sharing to take place concerning customisation of play space, toys and play routines to enrich the infant's learning environment. Measuring cognitive outcomes by motor manipulation of cognitive test items in infants with CP is complex and may have dampened our ability to detect cognitive change. Many items are dependent on age appropriate hand motor function and most widely used tools are not validated or sensitive to change in children with CP<sup>31</sup>. A recent study of 4-5 year olds with CP showed that almost 40% of participants were unable to complete enough items to score a complete IQ test due to difficulties with items requiring verbal ability and accurate fine motor performance (for example, pointing) <sup>32</sup>. It is likely that infants in this study with poor hand function may have scored lower than their actual ability. Measuring cognition accurately in children with severe forms of CP is an area requiring urgent research.

The high number of infants diagnosed with CP by 12 months (n=25; 83%) demonstrated the feasibility and accuracy of recruiting young infants with CP to clinical trials using Prechtl's General Movements Assessment (GMA)<sup>33</sup>. To our knowledge this is the first study published in literature to recruit a sample of young infants (<6 months) where over 80% had CP. The 2 infants not diagnosed with CP but whom had severe global delay (all domains <2 SDs below the mean) had absent fidgety movements at 12-16 weeks but non-specific changes on neuroimaging. The combination of term equivalent MRI and GMA at fidgety age is recommended to most accurately identify infants with the highest risk of CP, as neuroimaging alone is less sensitive<sup>34</sup>. Two infants in this study were performing within the normal range on the PDMS-2 and the BSID-III at 12 months although they both had persisting mild asymmetries and one had spastic catches bilaterally at the ankle. Another infant who had also scored in the normal range on the norm referenced tests, was predicted from imaging not to have CP was nevertheless diagnosed with mild spastic diplegia at 12 months. Defining clinical diagnostic criteria for this group of mildly affected infants is difficult and, in the absence of obvious activity limitations that are required for a diagnosis of CP<sup>1</sup>, clinicians are understandably reluctant to use the CP label. It is also a possibility that early motor intervention may have optimised the outcomes of these infants.

Parent satisfaction with and perception of their infant's performance on identified goals was clinically important at 12 months only in GAME but only significantly different from SC in satisfaction scores of the COPM. Interestingly this was different to results at the 16-week time point when performance scores were significantly higher for GAME families. Perhaps parent education about

CP in the GAME group led to parents being more realistic about their child's motor skills at 12 months.

Measuring home enrichment is complex and we attempted to do this by using a new scale, the AHEND-IS. Although not statistically significant, mean scores in the GAME group increased as a percentage of total possible score over the study period. This may indicate that parents in this group were more likely to provide a wider variety of learning materials to match motor challenge as their child developed. A limitation of the AHEND-IS is the focus on the physical home environment and variety of motor stimulation; it does not account for opportunities in other environments that the infant is exposed to. In addition, the scale does not capture parental responsiveness, a known contributor to child developmental outcomes<sup>35</sup>. Future studies of GAME should include measures of parental responsiveness as well as more responsive measures of the physical environment.

Professional mental health support was offered to all mothers with abnormal DASS-21 anxiety or depression scores at any time point. Parent mental health remained stable over the course of the study, with the mean score for depression in the "mildly abnormal" range both at baseline and after 16 weeks for mothers in GAME and in the normal range for SC. Although by 12 months mean scores for all subscales were in the normal range, approximately 20% of mothers were scoring in the moderate to severe range for depression and/or anxiety. This finding highlights the importance of the availability of evidence based parent support programmes for parents of infants newly diagnosed with disabilities<sup>36</sup>. In addition, two thirds of the sample was considered to be at high social risk plus one third were from families where English was not the first

language spoken at home. The combination of high social risk and higher than average levels of depression and anxiety amongst these mothers, highlights the vulnerability of families with young infants at high risk of CP and other disabilities. EI programmes should include family support options that assist parents in their role and provide strategies to support their mental health and enhance their well-being.

Previous CP trials in older children have shown that high-dose motor-learning based therapy leads to better results than low-dose motor-learning therapy, causing experts to hypothesise that many therapy interventions studied to date might be under-dosed. Interestingly, in older children, when two effective motor-learning interventions are compared head-to-head at the same high-dose, similar patient outcomes result. Recent systematic reviews have therefore identified that in addition to type of therapy mattering (effective versus ineffective) also the intensity of the therapy is important for treatment success<sup>37</sup>. In our GAME study, the dose of intervention was not statistically significant between the groups, due to the large variation within each group, however the median values clearly demonstrate that most GAME participants received a higher number of therapy sessions and most GAME parents engaged in more home practice. It is therefore likely that both the higher dose of intervention as well as characteristics of GAME contributed to the gains achieved in the GAME group.

#### Limitations

The study has a small sample size, but despite this we observed between-group differences. We estimated sample size on an earlier pilot study in which no infant had visual impairment. In this study the spread of severity was

considerably wider as evidenced by the confidence intervals in the primary outcome at follow up. In addition the n=4 dropout, all from the intervention group might have influenced the final results. A further limitation is the incomplete information about the intervention content of the SC group. As expected there was substantial variety in intensity, mode and type of therapy offered. Motor task practice and the provision of a home program were common elements across both groups. Future studies should endeavour to identify the specific elements of GAME that led to the demonstrated benefits. Finally, we used a novel severity variable to account for the variation in brain injury in our sample. This has not been previously tested however in this study it predicted outcome accurately 75% of the time which proved more accurate than the most recognised severity tool, GMFCS, which is 58% in this age group<sup>38</sup>.

## CONCLUSION

Our study suggests that 6-9 months of GAME, a clinically feasible intervention, is more effective than SC to advance the motor function of infants at high risk of CP. Furthermore using the GMA to recruit very young infants with CP to clinical trials is possible. GAME is a promising new early intervention for infants. We therefore recommend a larger and longer well-powered RCT of GAME intervention be conducted with more finely tuned exclusion and inclusion criteria to establish characteristics of responders and non-responders and to define the minimum dose required.

## ACKNOWLEDGEMENTS

We thank the children and their families who participated in this study and the Sydney Children's Hospital Network for assistance with recruitment. We acknowledge and sincerely thank Dr Kristina Prelog, Ms Jane Berry, Ms Prue Golland, Dr Petra Karlsson, Dr Karen Walker and Ms Salli-Ann Wilson for their assistance with blind scoring of infant and family assessments and neuroimaging data.

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Figure 1: Flow of participants

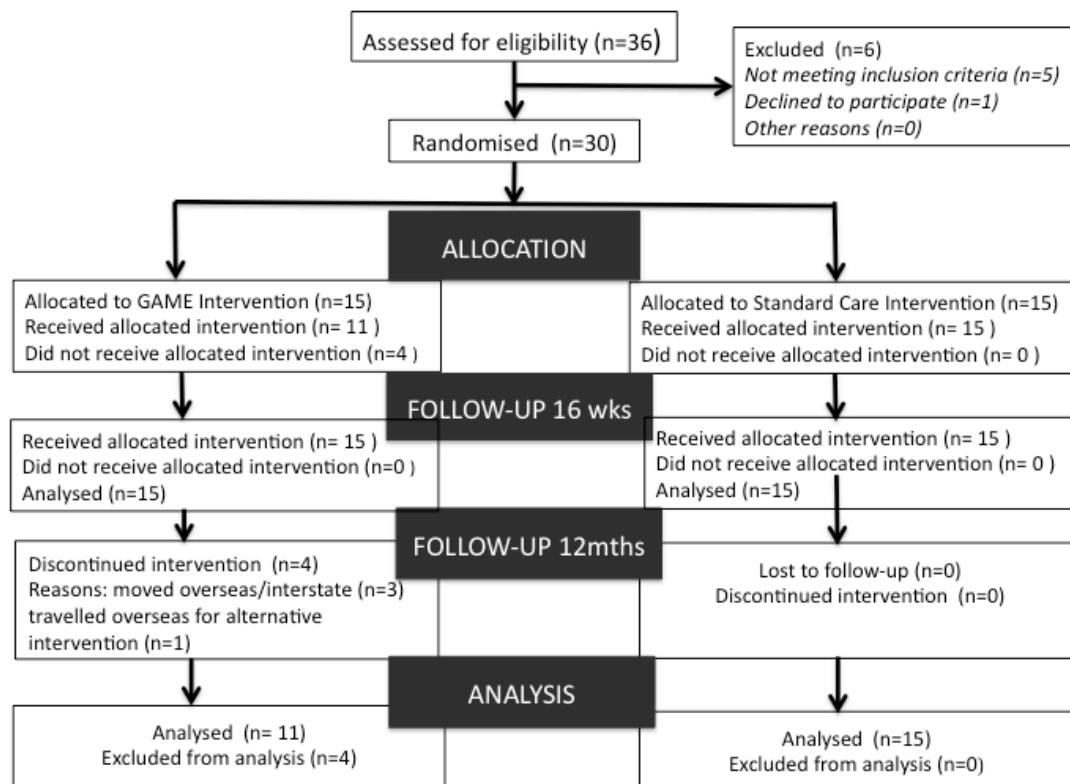


TABLE 1. Characteristics of Participants

INFANT CHARACTERISTICS		GAME n=15	SC n=15
AGE	Enrolment corrected age (weeks) mean (SD)	15.73 (4.76)	20.07 (5.08)*
SEX	Male, n (%)	8 (53)	9 (60)
CP RISK FACTORS	Birth weight (kg), mean (SD)	2.31 (1.02)	2.65 (1.12)
	Multiple births, n (%)	2 (13)	2 (13)
	Hypoxic Ischaemic Encephalopathy, n (%)	4 (27)	2 (13)
	Birth gestational age (weeks), mean (SD)	34.27(5.27)	35.27 (5.09)
	• < 28 weeks, n (%)	1(6)	1(6)
	• 28-31 weeks, n (%)	4(27)	3(20)
CP DETECTION	• 32-36 weeks, n (%)	2(13)	2(13)
	• > 36 weeks, n (%)	8(53)	9(60)
	GMs Absent fidgety, n (%)	15 (100)	13(87)
	GMs not assessed, n (%)	0	2 (13)
	Neuroimaging available, n (%)		
	<i>MRI</i>	13 (87)	12 (80)
	• <i>CUS only</i>	1 (6)	2 (13)
	• <i>No imaging</i>	1 (6)	1 (6)
	Neuroimaging results, n (%) ( <i>MRI or CUS – term equivalent age</i> )		
	• <i>Normal</i>	0	1 (6)
CP SEVERITY SCORES (predicted by blind scoring of imaging)	• <i>Unilateral injury</i>	1(6)	3(20)
	• <i>Bilateral injury</i>	13(87)	10(67)
	• <i>3=non-ambulant CP +VI</i>	4(27)	2(13)
	• <i>2 = non-ambulant CP no VI OR ambulant CP + VI</i>	4 (27)	1 (6)
	• <i>1 = ambulant CP no VI OR VI alone</i>	4 (27)	7 (47)
Associated impairments n (%)	• <i>0 = no CP and no VI</i>	2 (13)	4 (27)
	• <i>Missing (ie no imaging available)</i>	1 (6)	1 (6)
	• <i>Severe cerebral vision impairment (CVI)</i>	4(27)	3(20)
	• <i>Severe ROP (Grade 3)</i>	0	1(6)
	• <i>Epilepsy (uncontrolled)</i>	1(6)	1(6)
FAMILY CHARACTERISTICS	• <i>Hearing Impairment</i>	0	1(6)
	• <i>Microcephaly (&gt;3 SD below mean)</i>	5 (33)	3 (20)
	SOCIAL RISK		
	Maternal age; mean (SD)	33.73 (4.73)	31.07 (7.11)
SOCIAL RISK	Mother's education beyond secondary school, n (%)	10 (67)	6 (40)
	Primary language not English, n (%)	7 (47)	3 (20)
	High social risk, n (%)	9 (60)	11 (73)

\* p<.05; CP severity score based on neonatal imaging and visual function; VI=vision impairment (either severe ROP or diagnosed severe cerebral vision impairment [CVI]); \*=Statistically significant

Table 2: Outcomes at baseline, after 16 weeks and at 12 months

Outcome		Group		Estimate of Effect (95% CI)	p-value
Time Point	Measure	GAME (n=15) Mean (SD)	SC (n=15) Mean (SD)		
INFANT MOTOR DEVELOPMENT					
Baseline	PDMS-2				
	Raw	33.60(13.71)	41.93 (16.49)	-	.14
16-weeks	PDMS -2				
	Raw	73.20(36.40)	77.20 (44.25)	20.71 (1.66,39.76)	.03*
12-months	PDMS-2				
	Raw	124.64(55.98)	107.93 (51.11)	51.58 (26.64,76.52)	.01*
Baseline	PDMS-2				
	TMQ	84.87 (7.89)	82.93 (7.92)	-	.51
16-weeks	PDMS-2				
	TMQ	79.13(16.11)	71.93 (16.02)	7.58 (-1.37, 16.52)	.09
12 -months	PDMS-2				
	TMQ	72.64(17.75)	67.339 (16.12)	8.29 (0.13, 16.45)	.05*
PARENT PERCEPTION OF INFANT MOTOR PERFORMANCE-					
Baseline	COPM	3.05 (1.09)	3.19 (0.58)	-	.41
	Performance				
16-weeks	COPM	6.53 (2.08)	5.94 (2.56)	1.86 (0.58, 3.14)	.01*
	Performance				
16-week new	COPM	3.75 (1.48)	3.45 (1.15)	-	.53
	Performance				
12-months	COPM	6.64 (2.55)	4.54 (2.82)	1.61 (0.11, 3.34)	.07
	performance				
Baseline	COPM	5.18 (2.24)	4.40 (1.64)	-	.28
	Satisfaction				
16-weeks	COPM	6.80 (2.37)	6.19 (2.80)	0.35 (-1.35, 2.13)	.08
	Satisfaction				
16-week new	COPM	4.05 (1.89)	4.78 (2.51)	-	.53
	Satisfaction				
12-months	COPM	7.00 (2.45)	5.18 (2.82)	2.14 (0.40, 3.89)	.02*
	Satisfaction				
INFANT MOTOR FUNCTION					
12-months	GMFM-66	34.97 (13.42)	32.51 (9.99)	7.96 (0.00, 15.96)	.05*
INFANT DEVELOPMENT					
12-months	BSID-III				
	Cognition	6.27 (4.69)	4.40 (4.09)	3.85 (0.39,7.31)	.03*
12-months	BSID-III				
	Fine motor	5.18 (3.66)	3.80 (3.41)	3.01 (0.32,5.71)	.03*
12-months	BSID-III				
	Gross motor	3.36 (3.98)	3.00 (3.05)	5.72 (2.88, 8.56)	.12
HOME ENRICHMENT					
Baseline	AHEMD-IS	50.40 (14.08)	55.00 (11.83)	-	.34
12-months	AHEMD-IS	55.09 (13.90)	53.60 (10.66)	2.30 (-10.88, 6.30)	.59

PDMS-2= Peabody Developmental Motor Scales – Second edition; TMQ= total motor quotient; COPM=Canadian Occupational Performance Measure; GMFM-66= Gross Motor Function Measure; BSID-III= Bayley Scales of Infant and Toddler Development (expressed as standard scores); AHEMD-IS= Affordances in the Home Environment for Motor Development Infant Scale (expressed as percentage of total possible score). \*=Statistically significant

Table 3. Parent mental health at Baseline, after 16 weeks and at 12 months

<b>Measure</b>	<b>GAME Mean (SD)</b>	<b>SC Mean (SD)</b>	<b>p-value</b>
<b>DASS-21 Total Score</b>			
Baseline	29.60(21.26)	21.47(10.62)	.20
16 weeks	30.80 (24.92)	21.20 (17.95)	.24
12 months	22.73 (21.06)	19.20 (17.38)	.64
<b>Depression Sub-Scale</b>			
Baseline	10.67 (7.55)	4.53 (3.89)	.01*
16 weeks	10.00 (7.67)	6.27 (5.70)	.14
12 months	8.18 (7.13)	6.00 (7.13)	.45
<b>Stress Sub-Scale</b>			
Baseline	13.33 (9.58)	13.07 (5.60)	.93
16 weeks	14.27 (10.28)	9.87 (6.65)	.18
12 months	10.00 (10.51)	9.07 (6.50)	.78
<b>Anxiety Sub-Scale</b>			
Baseline	5.60 (6.29)	3.87 (4.69)	.40
16 weeks	6.53 (8.57)	5.07 (7.32)	.62
12 months	4.55 (5.52)	4.13 (6.07)	.86

\*=Statistically significant

# APPENDIX 1: PARTICIPANTS and OUTCOMES at 12 months

Infant sex	Group	CP risks and severity coding	GMs	Imaging Abnormalities (regions involved)	Diagnosis	Age diagnosed	Other impairments
1  F	SC	Preterm <32 weeks  Severity Code= 3	U F-	Bilateral GMI Bilateral PLIC involvement Pre-wallerian degeneration	CP Spastic bilateral	6 months	CVI Microcephaly Cognitive delay Epilepsy Gastrostomy
2  F	GAME	HIE IUGR  Severity code=2	PR F-	Extensive WMI Bilateral PLIC involvement Pre-wallerian degeneration	CP L unilateral	10 months	
3  M	GAME	Preterm <26 weeks  Severity code=2	PR F-	Bilateral Grade III/IV IVH Bilat cerebellar haemorrhages	CP R unilateral	8 months	CLD
4  M	GAME	Preterm <30 weeks Birth defect  Severity code=2	CS F-	Severe bilateral cPVL	CP Bilateral hypotonic	4 months	Microcephaly Cognitive delay
5  M	GAME	Birth defect  Severity code = missing	CS F-	No imaging	CP Mild dyskinetic unilateral	12 months	Cognitive delay
6  F	GAME	Preterm  Severity code=0	U F-	CUS Bilateral Periventricular echogenicity	CP Mild spastic bilateral	12 months	
7  M	SC	Preterm <26 weeks  Severity code=1	PR F-	CUS Periventricular echogenicity	CP Spastic bilateral	12 months	ROP stage 3
8  M	SC	CVA  Severity code=1	U U	Bilateral thalamic haemorrhages	CP Dyskinetic bilateral	10 months	Epilepsy Cognitive delay
9  M	SC	Birth defects  Severity code=0	CS F-	Signal intensity abnormalities Bilateral PLIC involvement	Global delay	NA	Hearing impairment Cognitive delay

10 M	SC	HIE  Severity code=2	PR F-	BGT injury + mild WMI Bilateral PLIC involvement	CP Bilateral Dyskinetic	8 months	
11 F	GAME	HIE  Severity code=1	PR F-	BGT injury Bilateral PLIC involvement	Spastic catches present both LLs, otherwise normal	Not diagnosed	
12 M	SC	Preterm  Severity code=0	PR F-	CUS Bilateral Gr III IVH Bilateral ventriculomeg aly	Mild asymmetr y, otherwise normal	Not diagnosed	
13 M	GAME	Preterm < 30 wks  Severity code=1	U F-	WMI Moderate bilateral cPVL	CP Spastic Bilateral	6 months	
14 F	SC	NNAS  Severity code=0	U	Normal	CP Mild spastic bilateral	5 months	Cognitive delay
15 M	GAME	HIE  Severity code=3	PR F-	Severe bilateral BGT and WMI	CP Bilateral dyskinetic	5 weeks	Epilepsy CVI Gastrostomy
16 F	GAME	Birth defects  Severity code=0	PR F-	Mild vermian hypoplasia Enlarged fourth ventricle	Unknown		Microcephaly Failure to thrive
17 F	SC	Birth defects  Severity code=1	PR F-	Maldevelopme nt: Reduced sulcation Abnormal ventricular shape	CP Bilateral	12 months	CVI Microcephaly Gastrostomy
18 M	SC	Hydrocephalus  Severity code=1	PR F-	Grade IV L IVH cPVL (left) L PLIC involvement	CP R unilateral	12 months	R hemianopia Severe feeding issues
19 F	SC	Preterm (<36 wks) NNAS Birth defects	PR F-	No imaging	CP Mild bilateral	12 months	

		Severity code= missing					
20 M	GAME	Preterm Multiple birth  Severity code=1	CH F-	Bilateral arterial infarction Bilateral PLIC involvement Pre- wallerian degeneration	CP Mild bilateral	12 months	
21 F	GAME	NE  Severity code=2	U F-	Bilateral BGT + WMI	CP Bilateral dyskinetic	8 months	
22 F	GAME	Nil known  Severity code=3	CS F-	Bilateral GMI + BGT Bilateral PLIC involvement	CP Bilateral spastic	5 months	CVI Microcephaly
23 M	GAME	Hydrocephalus Birth defects  Severity code=1	N F-	Bilateral ventriculomegaly Bilateral PLIC involvement	CP Bilateral spastic	10 months	
24 F	SC	HIE  Severity code=1	U F-	BGT + mild WMI	CP Mild Bilateral Spastic	12 months	
25 F	GAME	Preterm <30 weeks  Severity code=3	CH F-	Bilat GMI + BGT Severe bilateral cPVL Bilateral PLIC involvement	CP Bilateral dystonic	4 months	CVI Microcephaly Gastrostomy
26 M	SC	CVA  Severity code=1	U F-	L MCA infarct including BGT L PLIC involvement Pre-wallerian degeneration	CP Unilateral spastic	12 months	
27 M	SC	Seizures  Severity code=0	U F-	WMI + mild BGT Bilateral PLIC involvement	Global delay	Not diagnosed by 12 mths	Cognitive delay
28 M	SC	Preterm <30 weeks Multiple birth  Severity code=3	CS F-	Bilateral extensive WMI R IVH grade IV R PLIC involvement Pre-wallerian degeneration	CP Bilateral	4 months	CVI Microcephaly
29	SC	Preterm	CS	R GMI +	CP	8 months	

F		<30 weeks Multiple birth  Severity code=1	F-	thalamus R PLIC involvement Pre-wallerian degeneration	L unilateral		
30  M	GAME	Preterm <36 weeks Multiple birth  Severity code=3	PR F-	Severe bilateral cPVL Bilateral PLIC involvement	CP Bilateral spastic	4 months	CVI Microcephaly

GMs = general movements: U=unknown; PR= poor repertoire; CS= cramped synchronised; CH= chaotic; N=normal; F- = absent fidgety. HIE = hypoxic ischaemic encephalopathy; NE = neonatal encephalopathy; IUGR= intrauterine growth restriction; cPVL = cystic periventricular leukomalacia; NNAS = neonatal abstinence syndrome; CVA = cerebrovascular accident; CUS= cranial ultrasound; GMI= grey matter injury; WMI=white matter injury; BGT= basal ganglia and thalamus abnormalities; PLIC=posterior limb of internal capsule; MCA=middle cerebral artery infarction; IVH=intraventricular haemorrhage; CVI=cerebral vision impairment; ROP = retinopathy of prematurity; CLD = chronic lung disease



Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other <sup>†</sup> (details)
1.	<p><b>BRIEF NAME</b></p> <p>GAME (Goals, Activity, Motor Enrichment)</p>	1	Protocol; Pilot
2.	<p><b>WHY</b></p> <p>GAME is grounded in contemporary motor learning theory and is delivered in a family centred framework.</p>		Protocol; Pilot
3.	<p><b>WHAT</b></p> <p>All information relayed to families was customised to the parent's goals and questions and the infants needs. We did not use pre-written brochures or information sheets. Each family received a customised home programme containing activities and photographs of their child performing activities or how to "set up" play space for practice.</p> <p>A range of toys and learning materials were shown to the families and sometimes loaned to the family. Assistance was given to families who wanted to obtain specific toys for their child eg information re toy libraries, websites or shops to purchase additional materials. Wherever possible materials already owned by families was utilised.</p> <p>In most instances infant equipment (baby seats, prams or highchairs) already owned by the family was used or adapted. Customised foam inserts were sometimes used in highchairs to provide adequate support. Standing frames were provided to 2 infants with more severe motor impairments who could not take weight well in supported standing by 10 months.</p>		Protocol; Pilot

4. Therapy sessions: The time for sessions was usually set by parent preference according to the infant's routine. Usually all elements of GAME were present in every session. Motor training, parent education and environmental enrichment strategies were woven together. Sessions were modified around parent questions and infant health status, behavioural state or routine. Typically sessions began with discussion of changes since last appointment or any difficulties with activities. Therapist and parent problem solved solutions together.
- Motor training was customised to the child in relation to assessment and parent identified goals.
- Some examples of motor training:
- a) CIMT: infants with asymmetrical hand function were treated with modified CIMT from 6 months. A sock was used to constrain the affected hand. Suggested intensity of practice was 20 mins per day as tolerated. Parents were coached inappropriate activities for mCIMT as well as bimanual play.
  - b) Sit to stand: all infants practiced sit to stand activities with their parents. Initially this was from the parent's lap and as/if sitting balance progressed from a small foam block. This activity was integrated with reaching
  - c) Sitting: supported sitting began straight away both using a reclining infant seat with supports as required AND supported floor sitting. The minimal amount of support was provided and reduced as soon as infant demonstrated emerging ability to maintain balance. Activities to encourage reaching were introduced as early as practicable.
- Parent Education: General information about development, feeding, sleep, play and CP were given as questions arose -discussions could be initiated by either parent or therapist. Parents were coached in simple task analysis and in observation of movement principles.
- Home programme: Customised to infant; included range of activities related to each goal PLUS general information. Activity ideas were photographed. Programme updated as required

Protocol; Pilot

<b>WHO PROVIDED</b>		
5.	A physiotherapist and occupational therapist either together in a joint appointment or in individual sessions provided GAME intervention. Both therapists had more than 20 years experience in pediatric rehabilitation.	P 5 Protocol; pilot
<b>HOW</b>		
6.	All intervention was provided face to face on an individual basis.	P 5 Protocol; pilot
<b>WHERE</b>		
7.	GAME was always provided at the family's home.	P 5 Protocol; pilot
<b>WHEN and HOW MUCH</b>		
8.	GAME was offered at least fortnightly however some infants received weekly sessions for a portion of the study period. GAME dose was deliberately customized to the family's situation and preferences however no infant was offered therapy more than once per week. As there was variation in length of time in the study due to age of enrolment, we calculated both the mean and median of hours of therapy. Sessions were typically one hour in length but were customized to the situation and preferences of the family. Number of appointments ranged from 18 to 30 depending on age at enrolment and complexity of child and family. Length of sessions ranged from 30 minutes to 90 minutes	P 5 Protocol; pilot
<b>TAILORING</b>		
9.	As the infant developed adjustments were made to the programme to grade the challenge of the activity. Similarly if difficulties arose with feeding the infant was referred for further assessment.	Protocol; pilot

MODIFICATIONS	
<p><b>10.*</b> A number of infants were noted to have severe visual impairment. When this occurred the infant was referred for further assessment. The environment was adapted to include tactile and auditory toys and implementation of advice by vision specialists was integrated into the programme.</p>	
<p><b>HOW WELL</b></p> <p><b>11.</b> As the same therapist provided the intervention to all infants in the experimental group, fidelity was not separately assessed</p>	Protocol; pilot
<p><b>12.*</b> One infant in GAME went overseas for 8 weeks for family reasons during the intervention period and did not receive the intended dose of therapy. Four infants dropped out of the study between the 16 week and 12 month timepoints and for these infants the dose was not calculated as no logbooks were collected. Parents were not instructed how much to practice home programme activities with their infants at home but were asked to do as much as they felt they could manage. There was a big range of home practice recorded</p>	

**\*\* Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use ‘?’ if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

\* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

\* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see [www.consort-statement.org](http://www.consort-statement.org)) as an extension of **Item 5 of the CONSORT 2010 Statement**.

When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see [www.spirit-statement.org](http://www.spirit-statement.org)). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see [www.equator-network.org](http://www.equator-network.org)).

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other <sup>†</sup> (details)
1.	<b>BRIEF NAME</b> Standard Care	P1	Protocol; pilot
	Intervention information provided by parent questionnaire		
2.	<b>WHY</b> SC might have been based on NDT, sensory-integration, developmental skill or motor learning theory.	Appendix 2	Protocol; pilot
	<b>WHAT</b> SC was variable and all information in this appendix is based on parent questionnaire. All parents were given a home programme and for 1/3 this was provided in written format. Most parents were told how long and how often to carry out the HP. Sometimes photographs were used to demonstrate the HP. Some therapist recommended equipment such as highchairs, baby seating including Bumbo seats or an infant seat with tray. One third prescribed specialised seating. Four infants received standing frames while 6 used therapy balls for practicing set activities		
4.	Therapy sessions: Typically therapists handled the infant for practicing motor skills or facilitating movement. Two thirds of parents reported being active in the session, eg practicing activities after being shown. In a few instances the parent watched the session and was not involved in handling. Most parents reported receiving advice regarding feeding, and developmental simulation. About 40% reported being educated in stretches and exercises to be done during diaper changing and about one third were educated in optimal carrying positions. All participants' therapy was directed towards	Appendix 2	

<p>milestone attainment such as rolling, head control and reaching. One-third practiced sitting and one-third practice standing within therapy sessions.</p> <p><b>WHO PROVIDED</b></p> <p>5. A physiotherapist and/or occupational therapist of varying years of experience provided therapy. There were approximately 18 different therapists involved altogether with infants in SC. Appendix 2</p> <p><b>HOW</b></p> <p>6. Most intervention was provided face to face on an individual basis. A few infants attended group sessions eg hydrotherapy. Appendix 2</p> <p><b>WHERE</b></p> <p>7. SC was usually provided at a hospital outpatient setting or in a community setting. One third of infants had at least one home visit but no infant in SC had only home visits. Appendix 2</p> <p>Protocol; pilot</p>	
<p><b>WHEN and HOW MUCH</b></p> <p>8. SC was provided with a high degree of variability in intensity. Number of sessions during the study period (6-9 months) ranged from 2-45 sessions. Length of sessions ranged from 15 -90 minutes</p> <p><b>TAILORING</b></p> <p>9. This information was not collected for standard care, however it seemed from questionnaires that each child received a customised programme.</p> <p><b>MODIFICATIONS</b></p> <p>10.<sup>‡</sup> NA</p> <p><b>HOW WELL</b></p> <p>11. Fidelity not assessed – standard care variable as this was a pragmatic trial.</p> <p>12.<sup>‡</sup> One infant only received 2 sessions as development was on track. Another infant was hospitalised for 3 months however received inpatient intervention during this period when medically stable.</p> <p>Protocol; pilot</p>	

**\*\* Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use ‘?’ if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

# If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

\* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

\* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see [www.consort-statement.org](http://www.consort-statement.org)) as an extension of **Item 5 of the CONSORT 2010 Statement**.

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### Checklist of items to include when reporting a randomized trial (56-58)

PAPER SECTION And topic	Item	Description	Reported on page #
<i>TITLE &amp; ABSTRACT</i>	1	<a href="#">How participants were allocated to interventions</a> (e.g., "random allocation", "randomized", or "randomly assigned").	1,2
<i>INTRODUCTION</i> Background	2	<a href="#">Scientific background and explanation of rationale.</a>	3
<i>METHODS</i> Participants	3	<a href="#">Eligibility criteria for participants</a> and the <a href="#">settings and locations where the data were collected.</a>	4
Interventions	4	<a href="#">Precise details of the interventions intended for each group and how and when they were actually administered.</a>	5-6
Objectives	5	<a href="#">Specific objectives and hypotheses.</a>	Protocol
Outcomes	6	<a href="#">Clearly defined primary and secondary outcome measures</a> and, when applicable, any <a href="#">methods used to enhance the quality of measurements</a> (e.g., multiple observations, training of assessors).	6-7
Sample size	7	<a href="#">How sample size was determined</a> and, when applicable, <a href="#">explanation of any interim analyses and stopping rules.</a>	7-8
Randomization -- Sequence generation	8	<a href="#">Method used to generate the random allocation sequence,</a> including <a href="#">details of any restriction</a> (e.g., blocking, stratification).	5
Randomization -- Allocation concealment	9	<a href="#">Method used to implement the random allocation sequence</a> (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	5
Randomization -- Implementation	10	<a href="#">Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</a>	4-5
Blinding (masking)	11	<a href="#">Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment.</a> When relevant, <a href="#">how the success of blinding was evaluated.</a>	6-7
Statistical methods	12	<a href="#">Statistical methods used to compare groups for primary outcome(s);</a> <a href="#">Methods for additional analyses,</a> such as subgroup analyses and adjusted analyses.	8
RESULTS  Participant flow	13	<a href="#">Flow of participants through each stage</a> (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. <a href="#">Describe protocol deviations from study as planned, together with reasons.</a>	Figure 1
Recruitment	14	<a href="#">Dates defining the periods of recruitment and follow-up.</a>	9
Baseline data	15	<a href="#">Baseline demographic and clinical characteristics of each group.</a>	Table 1
Numbers analyzed	16	<a href="#">Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat"</a> . State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	9
Outcomes and estimation	17	<a href="#">For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision</a> (e.g., 95% confidence interval).	Tables 2 and 3
Ancillary analyses	18	<a href="#">Address multiplicity by reporting any other analyses performed,</a> including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	NA
Adverse events	19	<a href="#">All important adverse events or side effects in each intervention group.</a>	NA
DISCUSSION Interpretation	20	<a href="#">Interpretation of the results,</a> taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	12-17
Generalizability	21	<a href="#">Generalizability (external validity) of the trial findings.</a>	16-18
Overall evidence	22	<a href="#">General interpretation of the results in the context of current evidence.</a>	16-18



## Chapter 8 CONCLUSION

### 8.1 SUMMARY

The studies of this thesis make an innovative and important contribution to the early intervention in CP field. Despite the limitations outlined at the end of this chapter, GAME is a promising intervention for infants with CP and their families. The results demonstrate the importance of early diagnosis using the GMA, and the importance of testing of motor and cognitive outcomes of infants with CP in well-powered early intervention trials.

The studies of this thesis have focussed on two problems and investigated two solutions:

1. PROBLEM: Although the brain injury or lesion associated with CP originates in infancy and is non-progressive, a clinical diagnosis of CP is not usually given until the second year of life. Not identifying CP in infancy delays access to possible neuro-rehabilitative interventions that have the potential to harness neuroplastic mechanisms and optimise developmental outcomes.

SOLUTION: High quality evidence exists that in fact CP can be detected early in high risk infants if the right tools are used, namely the GMA and appropriately timed MRI (Study 1). The subsequent research programme confirmed that the GMA detects CP in 3-4 month old high-risk infants with high levels of sensitivity and specificity in an Australian context, similar to those published elsewhere and therefore is feasible (Study 3).

2. PROBLEM: There is a lack of empirical evidence that early intervention for infants at high risk of CP has benefits for motor outcomes above that which would have been expected from development. This problem in part flows from the historical difficulties in identifying the “right” infants to recruit to clinical trials. In addition, goal-oriented motor learning interventions known to be effective in older children with CP had not previously been tested in infants.

SOLUTION: Our systematic review (Study 2) found that interventions that include an environmental enrichment component have a small but positive effect on motor outcomes in infants at high risk of / with CP. We therefore next developed and tested an intervention ("GAME"), based on motor learning and environmental enrichment principles, in infants at high risk of CP, whom we recruited using the GMA or MRI (Studies 4-6). These two small clinical trials demonstrated that GAME is feasible to deliver and can advance the motor outcomes of infants with CP.

## 8.2 SYNTHESIS OF FINDINGS

### 8.2.1. *Early identification of CP - major findings*

#### *a) The right infants, the right tools at the right time*

The first two research questions (identified in Chapter 1 p ) asked if it was possible to detect CP in the first months of life and if it was, then what the most predictive tools were, and what was the feasibility of achieving this in our local context (Studies 1 and 3).

*Right infants:* The use of the right tools at the right time is the most accurate way of identifying those who are specifically at "high risk of CP" from those of generic "high-risk". More specific "high risk of CP" designation will enable infants to be offered diagnostic specific intervention rather than generalised developmental advice. For example, infants with unilateral lesions predictive of hemiplegia might be offered very early CIMT, while those with basal ganglia and thalamus lesions and thus at risk of severe dyskinetic CP, could be offered very early access to technology.

In Study 1 we summarised the risk profile for CP using data from the Australian Cerebral Palsy Register. The mean age of diagnosis of CP was 19 months. It was found that just over half of all children later diagnosed with CP were considered high risk in the neonatal period and were NICU patients. In this group a large proportion of infants were preterm, although amongst the preterm population 10% or less actually go on to have CP. Higher risk for CP exists for infants with neonatal encephalopathy,

particularly those with moderate to severe HIE, even with the advent of hypothermia (1).

*Right tools at the right time:* For infants in the high-risk group we have made recommendations for finding the right infants using the right tools, based on available evidence (Study 1). This includes the routine and systematic use of sensitive assessment tools including the GMA, HINE and neuroimaging (preferably MRI) within the NICU environment as well as GMA and HINE at follow-up. Identified infants should be referred for early intervention to promote development. These infants are at high risk of abnormal outcome on the basis of abnormal GMs alone. In our sensitivity study (Study 3) only three infants with abnormal fidgety movements had not received a definitive diagnosis at 12 months but had received early intervention and were being closely monitored due to mild neurological signs, such as asymmetry in hand function. All of the others had received early intervention and either had CP or another developmental disorder. This study confirmed that early detection is feasible in our context.

*b) Recruiting samples of infants with CP is possible*

Considering that CP is such a heterogeneous condition, and that 15% have normal MRIs, and that the GMA can also detect severe cognitive impairment, it is unlikely that 100% accuracy in detecting CP is achievable in the first year using even the best combination of tools. However, given that 50% of infants that will later be diagnosed with CP were treated in NICUs, earlier detection is achievable for many of these infants (2).

Prior to the targeted training of clinicians across all NICUs in NSW, only one centre was using the GMA routinely. As a result of our knowledge translation project (Study 3) that used tailored site-specific solutions to embed the use of the GMA into practice, all centres now have at least two trained staff and a number of centres have changed their follow-up schedule to take advantage of the optimal window for GMA. This simple shift in practice enabled accurate identification of infants suitable for enrolment into the RCTs of this research program as well as earlier access to intervention for other infants with identified delays.

In the two RCTs we conducted (Studies 5 and 6), the GMA was used to identify infants for recruitment to the trials. In the pilot study 85% were referred from NICUs and 15% from the community. In the 12-week pilot (Study 5) 77% of infants had a definitive diagnosis of CP before the primary endpoint. The long-term outcome of the others is unknown. In the larger RCT (Study 6) 83% had a definitive diagnosis by 12 months, 7% had severe developmental delay, 7% had normal outcomes on standardised testing but persisting mild asymmetries and 3% had dropped out prior to diagnosis. To our knowledge of the published literature, these two studies have recruited the highest percentage of infants with CP from such an early age. Future studies might be able to improve further on this by adopting inclusion criteria that specifies relevant MRI results and absent fidgety GMs at 3-4 months.

*c) Use of clinical imaging in prognosis*

Predicting CP from MRI is possible in many cases if the right timing, equipment, sequences and scorers are used (3). In the preterm population, MRI at term equivalent age has higher sensitivity for predicting CP than earlier scans and is recommended for these infants for risk stratification (4-6). For term born infants the picture is less clear, although in recent reviews authors have confirmed the sensitivity of early (newborn) MRI post HIE and neonatal stroke for predicting neurodevelopmental outcomes, including CP (3, 7).

In our second RCT (Study 6) a pediatric neurologist and radiologist blind scored clinical imaging and were 75% accurate in predicting a future diagnosis of ambulant or non-ambulant CP (Appendix 1 of chapter 7). Of the 25% of cases where the outcome was not accurately predicted from imaging alone, 7% was a scan quality issue (CUS) and 3% had a normal finding. A further 7% were expected from imaging to be non-ambulant due to extensive bilateral injuries but were clearly going to be ambulant by the 12-month assessment. Only one infant predicted to have ambulant CP was not diagnosed by 12 months. In essence, in our study, clinical imaging when scored by experts, gave enough information to predict CP and therefore we

conclude high quality imaging should be routinely included in the diagnostic process.

### **Implications for policy, practice and research**

1). *A multidisciplinary approach to the diagnostic process is recommended.*

Imaging experts, neonatologists and allied health practitioners are all responsible for aspects of infant care and assessment. Parents of high-risk infants need evidence-based information provided compassionately and in a timely fashion with which they can begin the process of acceptance of their child's disability.

2). *To most accurately make an early clinical diagnosis of CP both the GMA and MRI are recommended to be used.*

The combination of absent fidgety general movements and specific findings on MRI are highly predictive of CP and we recommend counselling for parents and prompt referral to early intervention programmes that offer motor learning and cognitive enrichment approaches. In cases where only general movements are abnormal but MRI findings are non-specific we recommend a "high-risk of CP" designation be given and an explanation to parents that a more formal diagnosis may be established in the future. Early intervention should still be offered in this case.

Clinicians responsible for the care of high-risk infants ought to be equipped with the most appropriate training to accurately identify the infants in their care most in need of intervention post discharge. Currently the use of neuroimaging appears "centre dependent". MRI is more often used for infants with HIE than preterm infants although well equipped centres might use MRI in more instances. Cranial ultrasound is the imaging of choice in the preterm population due to its clinical utility, however CUS has lower sensitivity and when used alone misses a large proportion of infants with CP (8-9). Routine use of the GMA within the NICU environment could identify those at neurological risk thus enabling closer specific monitoring. In particular, a trajectory of cramped synchronized general movements is a marker for later diagnosis of spastic CP (10) and could prompt a medical practitioner to request MRI. Infants with abnormal general movements ought

to be followed up and monitored even if other results such as imaging and early developmental testing are within the normal range. Further research to establish and implement the use of scoring systems for MRI at an international level is vital to further our understanding of causal pathways to CP and to ensure researchers and clinicians are using the same “language” when reporting neuroimaging findings.

*3). Neonatologists, paediatric neurologists, paediatricians and allied health personnel working with high-risk infants should receive basic training in the GMA.*

Currently, training in the GMA is not regarded as essential, however given the predictive validity of the assessment we recommend it be introduced. The human resource burden of GMA scoring might be reduced in the future by computerized scoring (13,14) as well as the development of smartphone applications to enable parents to record a general movements video and upload for scoring by certified assessors. Outcomes of these studies have the potential to improve clinical utility of GMA and when these tools are available should be seamlessly embedded into NICU and follow up environments.

*4). Standard neurological testing is an important part of the diagnostic process.*

Standard neonatal follow up includes comprehensive developmental assessment, typically using the BSID. Routine use of the HINE at follow up is a suitable addition to this procedure. Recent publications regarding the BSID have demonstrated poor predictive power for future cognitive and motor delays (11-12) and so should not be relied on in isolation to determine an infant’s neurodevelopmental status. We recommend the HINE be included for the high risk population as cut off scores on this assessment can predict CP at different time points with greater accuracy than other available tests. No specialized training course is required to be able to use this assessment.

*5). Identifying infants who are not regarded “high risk” in the neonatal period will prove more difficult.*

The causes of CP in the term born (“low risk”) group are still not well understood and lack of knowledge regarding timing of the injuries associated with CP is an ongoing problem. The “wait and see” approach is

commonly applied in practice, often leading to delay in referral for intervention and feelings of unresolved anxiety for parents (15). Another problem for this group is that there are very few CP-specific predictive tests. In infants older than six weeks an anaesthetic is usually required for MRI so in the absence of clear neurological signs, MRI is not typically offered. The atypical presence of primitive reflexes and muscle tone are considered basic items for infant assessment but are not as sensitive for prediction of neurodevelopmental outcome as the “quality and quantity of movement” items in the HINE (16). Assessment of risk factors, neurological exam (HINE) and standardized motor assessment and the use of the Ages and Stages Questionnaire with three additional questions are recommended, as outlined in Study 1. Further research is required to determine what combination of these items are the most predictive of a future diagnosis in “low risk” infants with motor delay.

In order to translate these recommendations into clinical practice we recommend that International Clinical Guidelines for the early detection of CP be developed and disseminated as a matter of urgency.

### *8.2.2. Early intervention for infants with CP – major findings*

#### *a) Infants with CP are an under-researched group*

The last three research questions (Chapter 1 p ) were focused on the effectiveness of using motor learning interventions for infants at high risk of CP. In Study 2 we used systematic review methodology to summarise the available evidence for the impact of environmental enrichment (EE) on the motor outcomes of infants with CP or at high risk of CP. The paucity of trials in this population was alarming with only seven RCTs retrieved from all published literature. Only the studies that included relatively homogeneous groups of infants with CP demonstrated between group differences in favour of the EE intervention group. These studies also included child-active motor training within the protocol.

The search process for this review demonstrated that although there were many intervention studies of preterm infants, very few of these studies included infants with known brain injuries and studies that included them had very low numbers with CP. In addition, interventions commonly researched in the “at risk” populations are now shown ineffective (17-18), while very few contemporary motor learning interventions have been tested in infants. We concluded that very little is known about the effect of early therapy intervention on infants at the highest risk of CP because despite commonly held beliefs, they are an under-studied population. Our meta-analysis (Study 2) was able to demonstrate, however, a small but positive effect for interventions that included environmental enrichment even though the types of enrichment varied between the studies.

*b) A motor-learning intervention, GAME is effective for infants with CP*

The intervention package we developed and labelled GAME (Study 4) was built upon published literature relating to goal and activity based therapy, motor-learning principles, and environmental enrichment and delivered in the context of family centred care. The protocol was first tested in a pilot study (Study 5) and we found the intervention was acceptable to parents and the recruitment processes were identifying the “right” infants. The second larger and longer RCT (Study 6) used slightly expanded inclusion criteria and some alternative outcome measures. Both of these studies demonstrated that early motor learning interventions, delivered in an enriched home environment and jointly applied by trained therapists and parents can improve motor outcomes of infants with CP to a greater extent than usual care. This is the first trial to demonstrate superior motor outcomes since Palmer’s trial (19), and is therefore a new contribution to knowledge about early intervention in CP.

Although there were elements of GAME and standard care (SC) that overlapped, for example provision of home programmes, GAME was unique in mode (100% home visits), content (active motor training focus versus milestone attainment focus) and total dose (on average 52 hours more than standard care in Study 6).



*c) Standard early intervention is variable in content and intensity*

Studies 5 and 6 confirmed that early intervention services for infants at high risk of CP in Sydney, Australia were extremely variable in mode, content and dose. Our earlier survey of a number of NICU staff found that infants in this category typically received about 14.2 hours of therapy during the first year of life (Appendix 1 of Chapter 1). This figure was very close to the 14.82 hours of therapy received by infants in standard care in Study 6 but is a vast contrast to the rehabilitation that adults with brain injuries receive. The National Institute for Health and Care Excellence (NICE) adult stroke guidelines (20) recommend a multidisciplinary team conduct assessments and provide intervention for every domain affected for at least 45 minutes per day, 5 days per week. If these guidelines were followed, an adult stroke patient receiving the recommended dose of physiotherapy, occupational therapy and speech pathology would receive in seven days the same amount as infants with brain injuries typically receive in a whole year. In Study 6 33% of standard care infants received five hours or less of intervention over the entire study period while 13% received more than 38 hours.

As well as variability in intensity, the content of standard care intervention was also variable. Parents reported the use of therapy techniques from a range of approaches including sensory integration and neurodevelopmental therapy as well as motor learning. In general, therapy sessions targeted milestone attainment and provided advice about positioning and handling. Finally no child in standard care received all of their visits in a natural environment. While 33% had some home visits, most therapy sessions were conducted in clinical settings.

*c) Very little is known about the motor trajectories of infants with CP*

Our clinical trials recruited a heterogeneous group of infants, at various levels of risk for CP but who nevertheless most often received a diagnosis of CP. Some infants had standard motor scores in the low average or average range at three months but were scoring in the “very poor” range at 12 months even with consistent therapy. Some included infants had very stable scores over time, while others showed a slower decline. Since both natural history and intervention studies in this age group of infants with CP are so

few, an expected average rate of change in raw scores on most tests such as the PDMS-2 has not been established nor could it be predicted. In other words, Study 6 confirmed that predicting outcomes in infants with CP by using norm referenced early motor assessments is imprecise. Criterion referenced tests such as the GMFM are important for prognostication but are not as useful for this purpose before two years. Suitable criterion referenced assessments of the upper limb are available for infants with unilateral CP (21) but not yet published for infants with bilateral upper limb involvement.

*d) Associated impairments of infants make the first year difficult*

Almost half of the participants in Study 6 had significant associated impairments that adversely influenced their participation in therapy. The most common associated impairment for infants was severe vision impairment. Seven (23%) infants had severe cortical vision impairment and one had severe retinopathy of prematurity. In most cases parents were not aware at the time of discharge that their baby's vision was a problem as they had seen an ophthalmologist who had assessed the eyes as "normal". Delayed vision assessment meant that appropriate vision stimulation was not provided until after six months of age in most cases.

In Study 6, 20% of the infants had severe feeding problems of which 80% needed nasogastric or gastrostomy feeding by 12 months. In addition many infants in both groups had gastro-oesophageal reflux that interfered with sleep, play and required medication and/or specialist intervention. Sleep was reported as difficult by almost all families whose baby also had a vision impairment or severe reflux.

The cumulative effects of sensory impairment, inadequate nutrition, pain and sleep deprivation appeared to further delay the development of these infants. Very often these issues were dealt with by a wide range of health professionals, across a range of services, resulting in a fragmented approach to care.

*e) Parents are vulnerable, but are essential partners in early intervention*

The early intervention protocol we used in Studies 5 and 6 involved training parents to observe motor development and practice activities with their baby to promote improvement in their motor skills. This was essential to achieving an adequate “dose” of therapy as per motor learning principles. Concurrently we monitored the mental health of these parents and found that a proportion were experiencing higher than average levels of depression, stress or anxiety that persisted to their child’s first birthday. Managing the balance of educating and involving parents in carrying out home programmes, while supporting their own emotional needs is important to establish. Parents need information and practical and emotional support while at the same time the development of a strong attachment with their baby is essential. It is unknown if early intervention expectations help or hinder mother-infant attachment, however all parents in our studies expressed a desire to “do something” to help their child develop. Since depression in mothers is a known contributor to poorer cognition in at-risk children (22), taking care of the emotional health and well being of parents of high-risk infants seems important.

**Implications for policy, practice and research**

*1. More high quality research in early intervention for infants with CP is essential to move the field forward.*

The lack of early intervention evidence in infants and toddlers with CP is alarming and has likely contributed to the high variability in practice evident in standard care for these children. More research funding needs to be urgently channelled into this area and researchers must collaborate in order to organise well-powered clinical trials that will move the field forward. Recruitment streams to early intervention CP trials have previously been limited by identification of the “right” participants, but as we have shown this does not need to be a problem.

We recommend a larger, RCT of GAME with a longer intervention period be conducted with more finely tuned inclusion and exclusion criteria and longer term follow up.

*2) Best practice clinical guidelines in early intervention are required*

Health practitioners working in early intervention need up to date information regarding the suitable content for infants with CP, and how this might differ from intervention for children with global delay. Despite the small amount of evidence available clinical practice guidelines ought to be developed as a matter of urgency. When high level RCT evidence is not available, guidelines ought to reflect what is known about motor learning and dosing so that infants with brain injuries have the best chance to optimise neuroplasticity during the critical period. Such a document would give invaluable information to managers and policy makers regarding appropriate resource allocation for these children

*3. Prospective longitudinal data is urgently needed*

In order to predict likely motor outcome earlier, a prospective longitudinal study is required. Prospectively collecting data of the emerging motor skills and musculoskeletal status of infants with/at high risk of CP will improve our understanding of early developmental trajectories and potentially lead to strategies to prevent secondary impairments such as contracture from occurring.

*4. Responsivity of available measurement tools should be established*

Until more is known about the sensitivity to change of commonly used assessments in the CP population, researchers will find it difficult to clearly demonstrate an intervention effect above that which might solely be due to development. Even CP specific assessments such as the GMFM-66 do not have data concerning the amount of change that is regarded as “clinically significant”. This is an important area requiring further research.

*5. Early assessment and intervention for infants with CP should be holistic*

Early intervention services for infants at high risk of CP ought to include early and systematic assessment of vision, nutrition and feeding, sleep and attend to parental wellbeing. Difficulties in any of these areas should be immediately and comprehensively addressed so that infants and families can focus on developing healthy attachment and promoting infant motor and cognitive development. This holistic service will require a concerted and deliberate effort on the part of the Department of Health and their

community partners to collaborate more deliberately and effectively to streamline waiting times for parents and remove barriers that lead to delayed diagnosis and access to appropriate intervention.

The National Disability Insurance Agency currently have a unique opportunity in Australia to provide appropriate funding packages to support families to receive the right type and dose of therapy for infants at the right time.

### **8.2.3 LIMITATIONS OF THE STUDIES**

Our pragmatic trials (Studies 5 and 6) were confounded by the realities of variable clinical practice. For example, since early intervention is universally accepted as standard of care, conducting RCTs with a pure control group (ie no intervention) was understandably regarded as unethical in our context. Moreover parents should be free to seek co-interventions for their infant according to their preferences, and this was the case in our RCTs (Studies 5 and 6). The effect of co-interventions was difficult to account for in our pragmatic trials, however every effort was made to try and identify the essential ingredients within the intervention protocols that differentiated them from each other.

In future GAME and early intervention studies, a more detailed description of the content of standard care would be ideal, but difficult to obtain as clinicians are free to use their preferred approaches to therapy. In Study 6 we used the Tidier guidelines to summarise the content of both interventions but due to the great variability within the standard care group this had limitations. Some overlap in content of standard care and GAME was unavoidable. The fidelity of GAME was assured as the same therapists delivered GAME intervention to all participants in the GAME group however this makes replication of the study difficult. A knowledge translation project is now required to train therapists in delivering GAME intervention. Future GAME studies ought to involve other therapists trained in GAME to minimise the potential bias of “therapist effect”.

Studies 5 and 6 were also limited by the size of the samples we recruited. Although our sample size was calculated on pilot data (Study 5), the heterogeneity of CP meant that infants in the larger RCT (Study 6) were more severely affected and therefore perhaps slower to respond to intervention than a “typical” CP sample. In addition, since GMFCS level is not determined by 12 months, the final motor function of these infants is unclear.

The motor measures we used in the studies are another limitation. As previously described there is a paucity of outcome measures with demonstrable sensitivity to change for infants with disabilities. We attempted to use a known responsive primary outcome measure (Goal Attainment Scaling) in the pilot work (Study 5) however found this unsatisfactory due to the variability and unpredictability in the rate of developmental change between the infants. The PDMS-2 was chosen as there was some sensitivity data in CP, albeit in toddlers, and it measured hand skills and mobility skills, both of which are commonly targeted in early intervention programmes.

#### **8.2.4 CONCLUSION**

This unique series of studies has demonstrated that a novel intervention, GAME improves the motor and cognitive abilities of infants with cerebral palsy. We have shown that by using the right tools at the right time, the right infants can be accurately identified and recruited to early intervention trials. This programme of research suggests more is possible in the field of early intervention for infants with CP and further research is warranted.

## 8.2.5 REFERENCES

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15 November 2011

Ms Catherine Morgan  
Cerebral Palsy Alliance  
PO Box 184  
Brookvale  
NSW 2100

Dear Ms Morgan,

**HREC reference number:** 11/CHW/126  
You must quote this number for all future correspondence

**Project title:** Optimising motor learning of infants at high risk of cerebral palsy using environmental and goal oriented interventions

**NSW Sites listed:** The Children's Hospital at Westmead  
Liverpool Hospital  
Westmead Hospital  
Royal North Shore Hospital  
Royal Prince Alfred Hospital  
Royal Hospital for Women

Thank you for submitting the above project for single ethical and scientific review. This project was first considered by the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC) at its meeting held on 5 August 2011. This HREC has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review.

This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Research Involving Humans* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise that the HREC has granted ethical approval of this research project. The documents reviewed and approved include:

Document	Version	Date
NEAF Application AU/1/40AA09	2	20 September 2011
Study Protocol	2.0	29 August 2011
Information Sheet – Master (encl.)	2	2011
Informed Consent Form for Parent or Guardian – Master (encl.)	2	2011

Document	Version	Date
Information Sheet – CHW (encl.)	-	2011
Consent Form – CHW (encl.)	-	2011
Telephone script (encl.)	-	2011
Advertisement (encl.)	-	2011

Please note the following conditions of approval:

1. This approval is for a PILOT study only.
2. Any references made to **The Children's Hospital at Westmead Ethics Committee** should be changed to the **Sydney Children's Hospitals Network Human Research Ethics Committee**.
3. The co-ordinating investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:
  - Unforeseen events that might affect continued ethical acceptability of the project.
4. Proposed changes to the research protocol, conduct of the research, or length of HREC approval, will be provided to the HREC for review in the specified format.
5. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
6. The co-ordinating investigator will provide an annual report to the HREC and at completion of the study. The annual report form is available on the Hospital's intranet and internet or from the Secretary.
7. Your approval is valid for 5 years from the date of the final approval letter. If your project extends beyond five years then at the 5 year anniversary you are required to resubmit your protocol, according to the latest guidelines, seeking the renewal of your previous approval. In the event of a project **not having commenced** within 12 months of its approval, the approval will lapse and reapplication to the HREC will be required.


Should you have any queries about the HREC's consideration of your project please contact Ms Righa Saroo, Secretary of the HREC on 9845 3017.

**You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained.**

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The HREC wishes you every success in your research.

Yours faithfully



Ms Righa Saroo

**Secretary,**

**Sydney Children's Hospitals Network Human Research Ethics Committee**

cc: Dr Iona Novak, University of Notre Dame, Australia  
Prof Nadia Badawi, Grace Centre for Newborn Care, CHW

ON 15/11/2011

**Optimising Motor Learning for Infants at High Risk of Cerebral Palsy (A Pilot study)**

**INFORMED CONSENT FORM FOR PARENT OR  
GUARDIAN**

Ms Cathy Morgan, Cerebral Palsy Alliance; PH: 0408205542  
Assoc/Prof Iona Novak, Cerebral Palsy Alliance Research Institute; PH: 0409078917  
Professor Nadia Badawi, Children's Hospital at Westmead; PH: 9845 2715  
Assoc/Prof Russell Dale, Children's Hospital at Westmead: PH: 98453404

I, *(Parent/Guardian's name)*

\_\_\_\_\_ of

*(address)* \_\_\_\_\_

☐ hereby consent to my child, *(child's name)*

\_\_\_\_\_ being a volunteer participant in the above research project and understand this will involve videoing of my child's movement and accessing my child's medical record including MRI results if available. I understand I will be asked to answer questions in relation to my child's development and my well being.

- I have read and understood the Information Sheet about this project and any questions have been answered to my satisfaction.
- I understand that I am free to withdraw from the study at any time and this decision will not otherwise affect my child's treatment at the Hospital or the Cerebral Palsy Alliance and understand if I withdraw, my data will be de identified and stored securely
- I understand that all information gathered by the researcher will be treated as strictly confidential.
- I understand that a code will be given to all participants to ensure that the risk of identification is minimised.
- I understand that the protocol adopted by the University Of Notre Dame Australia Human Research Ethics Committee for the protection of privacy will be adhered to and relevant sections of the *Privacy Act* are available at <http://www.nhmrc.gov.au/>

This project has been approved by XXXXXXXXX Ethics Committee. If you have any worries or questions about the study, please call the Research Ethics Manager, (xxxx), who is the Secretary of the Ethics Committee.

C. Morgan

Template Version 2.0

Consent form - pilot study

- I agree that any research data gathered for the study may be published provided my name or other identifying information is not disclosed.
- A signed copy of this document will be retained by the researcher

I would like a summary of the research findings to be sent to me via:

- ☐ Email                      Address:  
☐ Post (at the above address)

NAME OF CHILD: \_\_\_\_\_  
(Please print)

NAME OF PARENT OR GUARDIAN: \_\_\_\_\_  
(Please print)

SIGNATURE OF PARENT OR GUARDIAN: \_\_\_\_\_  
Date: \_\_\_\_\_

NAME OF WITNESS: \_\_\_\_\_  
(Please print)

SIGNATURE OF WITNESS: \_\_\_\_\_  
Date: \_\_\_\_\_

NAME OF INTERPRETER: \_\_\_\_\_  
(Please print)

SIGNATURE OF INTERPRETER: \_\_\_\_\_  
Date: \_\_\_\_\_

14<sup>th</sup> April 2011

Ms Cathy Morgan  
Cerebral Palsy Alliance  
PO Box 184  
Brookvale NSW 2100

Dear Ms Morgan,

**RE: Optimising motor learning of infants with cerebral palsy using environmental and goal oriented interventions**

Your research and ethics approval from Cerebral Palsy Alliance Human Research and Ethics Committees and the Board of Directors has been finalised.

Details of the approval are as follows:

- Project approval number **2011-04-03**. Please use this number in all subsequent correspondence to The Committee.
- Approval period April 2011 to April 2014
- Authorised research personnel :
  - Ms Cathy Morgan
  - Dr Iona Novak
  - Prof Nadia Badawi
- Approved documentation:
  - Please attach a footer *This study has been approved by the Cerebral Palsy Alliance Human Research Ethics Committee. If you have any complaints or reservations about the ethical conduct of this research you may contact the Ethics Committee on (02) 9479 7200 or [ethics@cerebralpalsy.org.au](mailto:ethics@cerebralpalsy.org.au) to the information statements and consent forms, labelling these version 1. Please send a copy of the final updated documents to the Ethics Committee. If you wish to change these in the future please send a copy to the Ethics Committee for review.*

Cerebral Palsy Alliance's Human Research Ethics Committee (HREC) is a fully constituted Ethics Committee in accordance with the *National Statement on Ethical Conduct in Research Involving Humans 2007*. The approval of this project is conditional upon your continuing compliance with the *National Statement*. Accordingly, it is the responsibility of the chief investigator/s to:

- Provide a summary of your progress on a yearly basis to the committee commencing April 2012. A final report on completion and notification of any publications from this project is also requested. Failure to submit required reports will result in withdrawal of consent for the project to continue.
- Advise the HREC immediately in writing of any serious adverse events occurring during the course of the research.
- Advise the HREC immediately of all unforeseen events that might affect continued ethical acceptability of the project.
- Advise the HREC of any proposed changes to the research protocol, research personnel, information statement or consent form. All proposed amendments must be addressed in writing to the HREC and must be approved by the HREC before continuation of the project.

- Advise the HREC immediately, providing reasons, if the research is discontinued prior to its completion.
- Request an extension of ethics approval should the project not be completed within the time period specified above.
- Ensure that copies of all signed consent forms are retained and made available to the HREC on request.
- Provide a copy of this letter to any internal/external granting agencies if requested.

The Research and Ethics Committees and Board of Directors wish you well with this important project. The Research Committee is particularly keen that any positive findings from your research are shared with the organisation so they can be applied as soon as possible.

Yours sincerely,



Deborah Hoffman, on behalf of

Cain Beckett  
Chair, Research and Ethics Committees  
Member of the Board of Directors, Cerebral Palsy Alliance  
*Cerebral Palsy Alliance's Ethics Committee is a NHMRC HREC: EC00402*



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CRICOS PROVIDER CODE: 01032F

19 April 2011

Ref. #: 011012S

Catherine Morgan  
10 Softwood Avenue  
Beaumont Hills NSW 2155

Dear Catherine,

I am writing to you in regards to your Full Risk Application for Ethics Clearance for your proposed research project, to be undertaken for the research component of your course at The University of Notre Dame Australia.

The title of the project is: "*Optimising motor learning of infants with cerebral palsy using environmental and goal oriented interventions.*"

Your proposal has been reviewed by the University's Human Research Ethics Committee, and based on the information provided has been assessed as meeting all the requirements as mentioned in the *National Statement on Ethical Conduct in Human Research* (2007). I am therefore pleased to advise that ethical clearance has been granted for this proposed study.

Please note the following conditions of approval which apply to your research project:

- Ethics approval for this project is valid for 3 years. Under the *National Statement* you are required to report on the project's progress on an annual basis and the first annual report is therefore due in April 2011. Once your project is completed you are required to complete the Annual Report as a Final Report on your project. You are also required to notify the HREC Executive Officer in writing if this project is abandoned. The Annual Report form can be found at: <http://www.nd.edu.au/research/hrec/apply.shtml>.
- As a researcher you are required to immediately report to the HREC Executive Officer anything which might warrant review of ethical approval of the project, including unforeseen events that might affect continued ethical acceptability and any complaints made by participants regarding the conduct of the project.
- If the design of the study, the choice of instrument, or its manner of administration is altered in any significant way as the study progresses, you are required to submit an amendment in regards to the changes for ethical consideration to the HREC. The Amendment Form can be found at: <http://www.nd.edu.au/research/hrec/apply.shtml>.

On behalf of the Human Research Ethics Committee, I wish you well with what promises to be a most interesting and valuable study.





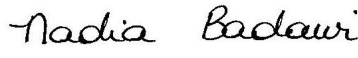

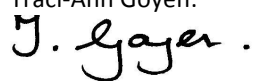



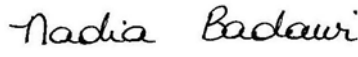
Yours sincerely,







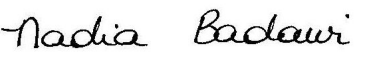




Dr Natalie Giles  
Executive Officer, Human Research Ethic Committee  
Research Office

Cc Professor Christine Bennett, Dean, School of Medicine  
Dr Iona Novak, Supervisor



## SIGNED AUTHOR CONTRIBUTIONS

PUBLICATION	AUTHORS CONTRIBUTIONS	AUTHOR SIGNATURES
McIntyre S, <b>Morgan C</b> , Walker K, Novak I. Cerebral palsy - don't delay. <i>Dev Disabil Res Rev.</i> 2011; <b>17</b> :114-29	All authors have participated in the concept and design of the paper and in drafting and revising the manuscript. Specifically: SM retrieved and analysed register data KW wrote the developmental section CM searched, critiqued and drafted the tools section IN drafted clinical practice algorithms	Sarah McIntyre: 
		Karen Walker 
		Iona Novak 
<b>Morgan C</b> , Novak I, Badawi N. Enriched environments and motor outcomes in cerebral palsy: systematic review and meta-analysis. <i>Pediatr.</i> 2013;132(3):e735-46.	CM and IN were involved in quality assessment, data extraction, data analysis, and manuscript preparation; NB was involved in quality assessment and manuscript critique. All authors were involved in study conception and design, interpretation of data, critical revision, and final approval of the submitted manuscript.	Iona Novak: 
		Nadia Badawi: 
<b>Morgan C</b> , Crowle C, Goyen TA, Hardman C, Jackman M, Novak I, Badawi N. Sensitivity and specificity of General Movements Assessment for diagnostic accuracy of detecting cerebral palsy in an Australian context. <i>JPCH</i> 2015	CM: Co-designed study, collated and analysed data, drafted manuscript and finalised for submission and review CC, TG, CH, MJ: Collected data and assisted in draft and revisions of manuscript IN & NB: participated in the concept and design of the paper and revising the original and revised manuscripts	Cathryn Crowle: 
		Traci-Ann Goyen: 
		Caroline Hardman: 
		Michelle Jackman: 
		Iona Novak: 
		Nadia Badawi: 

<p><b>Morgan C</b>, Novak I, Dale RC , Guzzetta A, &amp; Badawi N. GAME (Goals - Activity - Motor Enrichment): protocol of a single blind randomised controlled trial of motor training, parent education and environmental enrichment for infants at high risk of cerebral palsy. <i>BMC Neurol.</i> 2014; 14:(203).</p>	<p>CM and IN have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and have been involved in drafting the manuscript. NB, AG and RD have been involved in critically revising the manuscript for important intellectual content; and all authors have given final approval of the version to be published</p>	<div data-bbox="1011 192 1417 322">Iona Novak: </div> <div data-bbox="1011 322 1417 474">Russell C Dale: </div> <div data-bbox="1011 474 1417 613">Andrea Guzzetta: </div> <div data-bbox="1011 613 1417 734">Nadia Badawi: </div>
<p><b>Morgan C</b>, Novak I, Dale RC, &amp; Badawi N. Optimising motor learning in infants at high risk of cerebral palsy: a pilot study. <i>BMC Pediatr.</i> 2015; 15(1): 30.</p>	<p>CM and IN have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and have been involved in drafting the manuscript. NB and RD have been involved in critically revising the manuscript for important intellectual content; and all 4 authors have given final approval of the version to be published</p>	<div data-bbox="1011 734 1417 896">Iona Novak: </div> <div data-bbox="1011 896 1417 1064">Russell Dale: </div> <div data-bbox="1011 1064 1417 1227">Nadia Badawi </div>
<p><b>Morgan C</b>, Novak I, Dale RC, Guzzetta A, &amp; Badawi N. Phase 2 single blind randomised controlled trial of GAME (Goals - Activity - Motor Enrichment) in infants at high risk of cerebral palsy. <i>In press.</i></p>	<p>CM and IN have made substantial contributions to conception and design and acquisition of data. CM conducted data analysis and interpretation of data and drafted the manuscript. RD blind scored neuroimaging and AG assisted with blind scoring general movements assessments. IN, NB, RD and AG have been involved in critically revising the manuscript for important intellectual content; and all 5 authors have given final approval of the version to be published</p>	<div data-bbox="1011 1227 1417 1384">Iona Novak: </div> <div data-bbox="1011 1384 1417 1552">Russell Dale: </div> <div data-bbox="1011 1552 1417 1720">Andrea Guzzetta: </div> <div data-bbox="1011 1720 1417 1836">Nadia Badawi </div>

# A systematic review of interventions for children with cerebral palsy: state of the evidence

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This article is commented on by Msall on pages 877–878 of this issue.

## PUBLICATION DATA

Accepted for publication 5th June 2013.

## ABBREVIATIONS

COPM	Canadian Occupational Performance Measure
GAS	Goal Attainment Scaling
MACS	Manual Ability Classification System
NDT	Neurodevelopmental therapy

**AIM** The aim of this study was to describe systematically the best available intervention evidence for children with cerebral palsy (CP).

**METHOD** This study was a systematic review of systematic reviews. The following databases were searched: CINAHL, Cochrane Library, DARE, EMBASE, Google Scholar MEDLINE, OTSeeker, PEDro, PsycBITE, PsycINFO, and speechBITE. Two independent reviewers determined whether studies met the inclusion criteria. These were that (1) the study was a systematic review or the next best available; (2) it was a medical/allied health intervention; and (3) that more than 25% of participants were children with CP. Interventions were coded using the Oxford Levels of Evidence; GRADE; Evidence Alert Traffic Light; and the International Classification of Function, Disability and Health.

**RESULTS** Overall, 166 articles met the inclusion criteria (74% systematic reviews) across 64 discrete interventions seeking 131 outcomes. Of the outcomes assessed, 16% (21 out of 131) were graded 'do it' (green go); 58% (76 out of 131) 'probably do it' (yellow measure); 20% (26 out of 131) 'probably do not do it' (yellow measure); and 6% (8 out of 131) 'do not do it' (red stop). Green interventions included anticonvulsants, bimanual training, botulinum toxin, bisphosphonates, casting, constraint-induced movement therapy, context-focused therapy, diazepam, fitness training, goal-directed training, hip surveillance, home programmes, occupational therapy after botulinum toxin, pressure care, and selective dorsal rhizotomy. Most (70%) evidence for intervention was lower level (yellow) while 6% was ineffective (red).

**INTERPRETATION** Evidence supports 15 green light interventions. All yellow light interventions should be accompanied by a sensitive outcome measure to monitor progress and red light interventions should be discontinued since alternatives exist.

Thirty to 40% of interventions have no reported evidence-based and, alarmingly, another 20% of interventions provided are ineffectual, unnecessary, or harmful.<sup>1</sup> The gap between research and practice has been well documented in systematic reviews<sup>1</sup> across multiple diagnoses, specialties, and countries. Surveys confirm that, unfortunately, the research–practice gap occurs within the cerebral palsy (CP) field to the same degree.<sup>2,3</sup> This gap exists despite numerous systematic reviews providing guidance about what does and does not work for children with CP. When clinicians want to help, families expect effective interventions, and the health system depends upon cost-effective services, the provision of ineffectual interventions is illogical. In view of this, why is there such variable uptake of best available evidence within real clinical practice?

In the last decade, the CP evidence base has rapidly expanded, providing clinicians and families with the

possibility of newer, safer, and more effective interventions. Orthopaedic surgery and movement normalization were once the mainstays of intervention, but localized antispasticity medications and motor learning interventions have gained increased popularity.<sup>4,5</sup> Thus, the sheer volume of research published makes it hard for clinicians to keep up to date.<sup>6</sup> Systematic reviews seek to provide evidence summaries, but, in spite of this, clinicians find it difficult to interpret review findings and stay abreast of these syntheses.<sup>7</sup> Furthermore, the introduction of new and sometimes competing effective interventions increases the complexity of clinical reasoning required by clinicians, who are primarily motivated to improve outcomes for children.<sup>8</sup>

In the last 10 years, the field has adopted the World Health Organization's International Classification of Functioning, Disability and Health (ICF),<sup>9</sup> which has redefined the way clinicians understand CP and think about inter-

vention options. From an ICF perspective, CP impacts on a person's 'functioning', (inclusive of body structures [e.g. limbs], body functions [e.g. intellectual function], activities [e.g. walking], and participation [e.g. playing sport]), which in turn may cause 'disabilities', such as impairments, activity limitations, and participation restrictions. Moreover, each person with CP lives within a personalized environment and thus their context also contributes to determining their independence, comprising personal factors (e.g. motivation) and environmental factors (e.g. architectural accessibility).<sup>9,10</sup> Thus, there are many potential problems a child with CP may face and seek intervention for. The field has chosen a philosophical shift away from almost exclusively redressing physical impairments underlying functional problems to adopting an additional focus on maximizing children's environment, their independence in daily activities, and their community participation.<sup>11</sup> Furthermore, clinicians applying the recommended goal-based approach seek to choose interventions guided by what would best help the family achieve their goals.<sup>12–14</sup> Couple these philosophical preferences with widespread barriers to research implementation (such as limited time, insufficient library access, limited research appraisal skills, attitudinal blocks to research, and differing patient preferences), and there is no assurance that children with CP will receive evidence-based interventions.<sup>1,15,16</sup>

The aim of this paper was to describe systematically the best available evidence for CP interventions using the GRADE<sup>17</sup> system and to complement these findings with the Evidence Alert Traffic Light System<sup>18</sup> in order to provide knowledge translation guidance to clinicians about what to do. The purpose of rating the whole CP intervention evidence base within the one paper was to provide clinicians, managers, and policy-makers with a 'helicopter' view of best available intervention evidence that could be used to (1) inform decision-making by succinctly describing current evidence about CP interventions across the wide span of disciplines involved in care; (2) rapidly aid comparative clinical decision-making about similar interventions; and (3) provide a comprehensive resource that could be used by knowledge brokers to help prioritize the creation of knowledge translation tools to promote evidence implementation.<sup>19</sup>

## METHOD

### Study design

A systematic review of systematic reviews (i.e. the highest level of CP intervention research evidence available) was conducted in order to provide an overview of the current state of CP intervention evidence. Systematic reviews were preferentially sought since reviews provide a summary of large bodies of evidence and reviews help to explain differences among studies. Moreover, reviews limit bias which assists clinicians, managers, and policy-makers with decision-making about current best available evidence.<sup>20</sup> However, for interventions for which no systematic reviews existed, lower levels of evidence were included to illuminate the current state of the evidence.

### What this paper adds

- Of 64 discrete CP interventions, 24% are proven to be effective.
- 70% have uncertain effects and routine outcome measurement is necessary.
- 6% are proven to be ineffective.
- Effective interventions reflect current neuroscience and pharmacological knowledge.
- All effective interventions worked at only one level of the ICF.

### Search strategy

Our review was carried out using a protocol based upon recommendations from the Cochrane Collaboration and PRISMA statements.<sup>21,22</sup> Relevant articles were identified by searching the CINAHL (1983–2012); Cochrane Database of Systematic Reviews (1993–2013; [www.cochrane.org](http://www.cochrane.org)); Database of Reviews of Effectiveness (DARE); EMBASE (1980–2012); ERIC; Google Scholar; MEDLINE (1956–2012); OTSeeker ([www.otseeker.com](http://www.otseeker.com)); Physiotherapy Evidence Database (PEDro [[www.pedro.fhs.usyd.edu.au](http://www.pedro.fhs.usyd.edu.au)]); Psychological database for Brain Impairment Treatment Efficacy (PsyncBITE [[www.psycbite.com](http://www.psycbite.com)]); PsycINFO (1935–2012); PubMed; and Speech Pathology Database for Best Interventions and Treatment Efficacy (speechBITE [[www.speechbite.com](http://www.speechbite.com)]). Searches were supplemented by hand searching. The search of published studies was performed in July and August 2011 and updated in December 2012. Interventions and keywords for investigation were identified using (1) contributing authors' knowledge of the field; (2) internationally recognized CP websites such as the American Academy of Cerebral Palsy and Developmental Medicine ([www.aacpdm.org](http://www.aacpdm.org)), *CanChild* ([www.canchild.ca](http://www.canchild.ca)), the Cerebral Palsy Alliance ([www.cerebralpalsy.org.au](http://www.cerebralpalsy.org.au)), Cincinnati Children's Hospital ([www.cincinnatichildrens.org](http://www.cincinnatichildrens.org)), Karolinska Institutet ([www.ki.se](http://www.ki.se)), NetChild ([www.netchild.nl](http://www.netchild.nl)), NeuroDevNet ([www.neurodevnet.ca](http://www.neurodevnet.ca)), and Reaching for the Stars ([www.reachingforthestars.org](http://www.reachingforthestars.org)); and (3) the top 20 hits in Google using the search term 'cerebral palsy' as an indicator of popular subject matter.

Electronic databases were searched with EBSCO host software using PICO [patient/problem, intervention, comparison, and outcome] search terms. The full search strategy is available from the authors on request.

### Inclusion criteria

Published studies about intervention for children with CP fulfilling criteria under the headings below were included.

### Type of study

First, studies of level 1 evidence (systematic reviews), rated using the Oxford 2011 Levels of Evidence were preferentially sought.<sup>23</sup> The Oxford 2011 Levels of Evidence for treatment benefits include level 1, a systematic review of randomized trials or *n*-of-1 trials; level 2, a randomized trial or observational study with dramatic effect; level 3, a non-randomized controlled cohort/follow-up study; level 4, a case series, case-control study, or a historically controlled study; and level 5, mechanism-based reasoning.

Evidence of Oxford levels 2 to 4 were included only if (1) level 1 evidence did not exist on the topic and then the next best available highest level of evidence was included; or if (2) level 2 randomized controlled trial(s) had been published since the latest systematic review, which substantially changed knowledge about the topic.

Second, retrieved bodies of evidence were coded using the GRADE<sup>17</sup> system and Evidence Alert Traffic Light System<sup>18</sup> using two independent raters, with 100% agreement reached. The GRADE<sup>17</sup> system was chosen because it is a criterion standard evidence-grading tool and is endorsed by the World Health Organization. Definitions of the GRADE terms appear in the notes to Table I and a full description of panel rating processes are available from [www.gradeworkinggroup.org/publications/JCE\\_series](http://www.gradeworkinggroup.org/publications/JCE_series) (retrieved 8 March 2013). Notably, the GRADE system rates both (1) the quality of the evidence (randomized trials, high; observational studies, low; and other levels of evidence, very low, but it is worth mentioning that high-quality evidence is downgraded if methodological flaws exist and low-quality evidence is upgraded if high and certain effect sizes exist [e.g. population-based CP register data])<sup>17</sup> and (2) the strength of the recommendation for use, which weighs up trade-offs between the benefits and harms of using the intervention, whereby a panel considers (a) the methodological quality of the evidence supporting estimates of likely benefit and likely risk; (b) inconvenience; (c) the importance of the outcome that the treatment prevents; (d) the magnitude of the treatment effect; (e) the precision of the estimate of the treatment effect; (f) the risks associated with therapy; (g) the burdens of therapy; (h) the costs; and (i) the varying values.<sup>17</sup> The GRADE methodology means that sometimes bodies of evidence may be assigned a strong recommendation even when the quality of the evidence is low. This is either because there is a high likelihood of harm from no intervention (e.g. anti-convulsants to prevent seizures or ulcer prevention pressure care) or because the treatment has a low effect size and is expensive to provide, but a safe, more effective, cost-comparable alternative exists (e.g. phenol vs botulinum toxin A; or neurodevelopmental therapy [NDT] vs motor learning). The Evidence Alert Traffic Light System<sup>18</sup> was chosen because it is a GRADE-complementary knowledge translation tool, designed to assist clinicians to obtain easily readable, clinically useful answers within minutes.<sup>6</sup> The Evidence Alert also provides a simple, common language between clinicians, families, managers, and funders, based upon three-level colour coding that recommends a course of action for implementation of the evidence within clinical practice. The Evidence Alert System<sup>18</sup> has been shown to increase by threefold clinicians' reading habits about CP research.<sup>24</sup> Figure 1 describes the GRADE system and the Evidence Alert System and their relationship to each other. Table I shows the included studies, best evidence levels grades and traffic light classification.<sup>25–185</sup>

Where multiple systematic reviews existed and newer level 1 to 2 evidence superseded the findings of earlier level 1 evidence, the grades were assigned based on the most recent high-quality evidence.

### ***Types of intervention***

Studies were included if they involved the provision of and intervention by either a medical practitioner or allied health professional.

### ***Types of participants***

Studies were included if they explicitly involved human participants and more than 25% of the participants were children with CP.

Studies were excluded from the review if (1) they were diagnostic studies, prognostic studies, or interventions aimed at preventing CP (e.g. magnesium sulphate<sup>186</sup> and hypothermia<sup>187</sup>); (2) they provided lower levels of evidence, unless no systematic review had been published; (3) participants were adults, although if a study predominantly (>75%) studied children but included a small proportion of young adults (<25%) the paper was included; (4) they reviewed generic prophylaxis interventions (e.g. good parenting, standard neonatal care for all infants, i.e. not CP-specific interventions); (5) they reviewed a whole discipline, not individual interventions (e.g. physiotherapy, occupational therapy, speech pathology); (6) they were considered alternative and complementary interventions with no published evidence; (7) a second publication of the same study published the same results; and (8) they were unpublished or not peer reviewed.

### ***Data abstraction***

A data abstraction sheet based on the Cochrane's recommendations<sup>21</sup> was developed. Abstracts identified from searches were screened by two independent raters (CP research experts and knowledge brokers) to determine their eligibility for further review. Abstracts were retained for full review if they met the inclusion criteria or if more information was required from the full text to confirm that the study met all the eligibility criteria. Two independent reviewers then reviewed full-text versions of all retained articles and all additional articles identified by hand searching. Full-text articles were retained if they met inclusion criteria. Agreement on inclusion and exclusion assignment of the full-text articles was unanimous. Data extracted from included studies comprised the authors and date of the study; the type and purpose of the intervention implemented; the study design; the original authors' conclusions about efficacy across study outcomes; and the original authors' conclusions on strength of evidence (based on their assessment of whether there was no evidence of benefit, qualified support, or strong support). For lower level evidence, risk of bias was assessed using the Cochrane criteria.

The data extracted from each included study were summarized, tabulated, and assigned a level of evidence rating



**Table 1:** Included studies, best available evidence levels, grades and traffic lights

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	GRADE			Traffic light action
				Oxford evidence level	Quality of evidence	Strength of recommendation	
1 Acupuncture: electro-stimulation to scalp and body via needles and manual pressure	Improved gross motor function (A)	Zhang <sup>25</sup>	Insufficient evidence	1	Low	Weak +	Yellow MEASURE
2 Alcohol: muscular injections to induce chemical denervation for treating local spasticity	Reduce muscle spasticity locally via injections (BS)	Delgado <sup>26</sup>	Insufficient evidence to support, but BoNT-A exists as a highly effective alternative – therefore probably do not use alcohol unless BoNT-A total dose limitations in play	1	N/A	Weak –	Yellow MEASURE
3 Alternative and augmentative communication: technology alternatives to verbal speech, e.g. communication boards, speech generating devices	Improved general communication skills (A) Improved communication skills of pre-school children (A) Improved communication skills of conversational partners (P) Enhanced supplementation of verbal speech (A)	Pennington <sup>27</sup> Branson <sup>28</sup> Pennington <sup>29</sup> Hanson <sup>30</sup> Miller <sup>31</sup> Muñoz Lasa <sup>32</sup>	Lower-quality supporting evidence Lower-quality supporting evidence Lower-quality supporting evidence Lower-quality supporting evidence Lower-quality supporting evidence	1 1 1 1 1 1	Very low Very low Very low Very low Very low	Weak + Weak + Weak + Weak + Weak +	Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE
4 Animal-assisted therapy: service animals to provide companionship and assist with independence, e.g. seizure first aid, door opening, crossing roads	Improved socialization and mood; reduced stress, anxiety and loneliness; and improved leisure (BS and P) Improved independence via service dogs (P)	Winkle <sup>33</sup>	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
5 Anticonvulsants: medications to prevent seizures	Improved seizure control (BS)	–	No evidence in CP. Since high quality evidence exists in non-CP populations and there are high risks of adverse events from uncontrolled seizures therefore – do use anticonvulsants	–	N/A	Strong +	Green GO
6 Assistive technology: equipment or devices to improve independence e.g. walking frames, wheelchairs, adapted computer access	Improved independence in activities of daily living (A and P) Improved computer access via a switch or key guard (A) Improved independence in early mobility via powered wheelchairs (A and P) Improved participation in education, communication and play via alternative computer access (P) Improved function via robotic training or virtual reality (A)	Wilson <sup>34</sup> Davies <sup>35</sup> Jones <sup>36</sup> Livingstone <sup>37</sup> Chantry <sup>38</sup> Sandlund <sup>39</sup> Laufer <sup>40</sup> Parsons <sup>41</sup> Sandlund <sup>39</sup> Snider <sup>42</sup> Wang <sup>43</sup> Jung <sup>44</sup>	Lower-quality supporting evidence Lower-quality supporting evidence Lower-quality supporting evidence Lower-quality supporting evidence Lower-quality supporting evidence Lower-quality supporting evidence	2 1 2 1 1 1 1 1 1 1 1	Low Very low Low Very low Very low Very low Very low Very low Very low Very low Very low	Weak + Weak + Weak + Weak + Weak + Weak + Weak + Weak + Weak + Weak + Weak +	Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE
7 Baclofen (oral): antispasticity medication	Improved transfers via a hoist (A) Improved weight bearing and bone mineral density via a standing frame (BS) Improved sleep positioning via a sleep system (BS) Reduced carer burden (E) Reduced spasticity (BS)	Pin <sup>45</sup> Wynn <sup>46</sup> Nicolson <sup>47</sup> Delgado <sup>26</sup>	Insufficient evidence Insufficient evidence Lower-quality supporting evidence Lower-quality supporting evidence Lower-quality supporting evidence	1 1 1 1 1	Low Very low Very low Very low Very low	Weak + Weak + Weak + Weak + Weak +	Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE Yellow MEASURE

Table 1: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE		Traffic light action
					Quality of evidence	Strength of recommendation	
8	Behaviour therapy: positive behavioural support, behavioural interventions, and positive parenting	Improved child behaviour (from the Stepping Stones Triple P Programme) (A) Improved parenting skills (E)	Roberts <sup>48</sup> Sanders <sup>49</sup>  Whittingham <sup>50</sup>	Effective, but low CP numbers were included in the study samples and publication bias existed  Insufficient evidence	2 2	Weak +	Yellow MEASURE
9	Bimanual training: repetitive task training in the use of two hands together	Improved hand function, i.e. bilateral hand use for children with hemiplegia (A)	Gordon <sup>51</sup> Sakzewski <sup>4</sup> Sakzewski <sup>52</sup>	Effective. Equal effectiveness to constraint-induced movement therapy	2 1	Weak +	Yellow MEASURE
10	Biofeedback: electronic feedback about muscle activity to teach voluntary control	Improved muscle activation and active range of motion (BS) Improved walking (A)	Dursun <sup>53</sup>  Dursun <sup>53</sup>  Bloom <sup>54</sup>	Effective if combined with other treatments  Insufficient evidence  Lower-quality supporting evidence	2  2 4	Weak +  Weak +	Yellow MEASURE  Yellow MEASURE Yellow MEASURE
11	Bisphosphonates: medication to suppress bone reabsorption to treat osteoporosis	Improved bone mineral density (BS)	Fehlings <sup>55</sup> Hough <sup>36</sup>	Effective. Small RCTs suggest a positive effect and there are high risks of adverse events from no treatment	1 1	Strong +	Green GO
12	Botulinum toxin (BoNT-A): medication injected into overactive spastic muscles to locally block spasticity	Reduced lower limb muscle spasticity (BS)	Ade-Hall <sup>57</sup> Albavera-Hernandez <sup>58</sup> Boyd <sup>59</sup> Heinen <sup>60</sup> Koog <sup>61</sup> Lukban <sup>62</sup> Love <sup>63</sup> Mulligan <sup>64</sup> Fehlings <sup>65</sup> Reeuwijk <sup>66</sup> Wasiak <sup>67</sup>	Effective and safe	1 1	Strong +	Green GO
		Reduced upper limb muscle spasticity (BS)		Insufficient evidence. Note: function was preferentially measured over spasticity reduction in high quality studies. Since the drug is highly effective in lower limb muscles, we expect comparable results – therefore do use BoNT-A	1 1 1	Strong +	Green GO
		Reduced hypertonia of the neck muscles (BS)		Insufficient evidence. Since high-quality evidence supports tone reduction in primary dystonia (non-CP populations), we expect similar results – therefore probably do use BoNT-A	1	Weak +	Yellow MEASURE
		Improved walking function (A)	Novak <sup>68</sup>  Koog <sup>61</sup> Love <sup>63</sup> Ryll <sup>69</sup>	Probably effective in combination with physiotherapy therefore do use	1 1 1	Strong +	Green GO
		Improved hand function and performance of functional hand activities (A)	Boyd <sup>59</sup> Fehlings <sup>65</sup> Hoare <sup>70</sup> Hoare <sup>71</sup> Rawicki <sup>72</sup>	Effective in combination with occupational therapy	1 1 1 1	Strong +	Green GO
		Reduced pain (BS)		Insufficient evidence	1	Weak +	Yellow MEASURE
		Reduced drooling (BS)	Lim <sup>73</sup> Reddi <sup>74</sup> Walshe <sup>75</sup>	Effective short term and given the adverse social outcomes from no treatment – do use	1 1 1	Strong +	Green GO

Table 1: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE		Traffic light action
					Quality of evidence	Strength of recommendation	
13 Casting: Plaster casts applied to limbs to (a) stretch muscles for muscle lengthening, i.e. contracture reduction casts changed regularly; or (b) reduce spasticity	Improved passive range of motion of the lower limbs (BS)  Improved passive range of motion of the upper limbs (BS)  Improved function (A)	Autti-Ramo <sup>76</sup> Blackmore <sup>77</sup> Effgen <sup>78</sup> Katalinic <sup>79</sup>  Autti-Ramo <sup>76</sup> Lannin <sup>80</sup> Teplicky <sup>81</sup>  Autti-Ramo <sup>76</sup> Blackmore <sup>77</sup> Effgen <sup>78</sup>  Katalinic <sup>79</sup> Blackmore <sup>77</sup>	Effective. Gains in ankle range of motion are very small but are potentially clinically meaningful for children that need more dorsiflexion to walk, therefore – do use  Insufficient evidence  Insufficient evidence  Effective but gains are small	1 1 1 1 1 1 1 1 1 1 1 1	Low  Low  Low  Low  Low  Low  Low	Strong +  Weak +  Weak –  Weak +  Weak –  Weak +  Weak –  Weak +	Green GO  Yellow MEASURE  Yellow MEASURE  Green GO  Yellow MEASURE
14 Coaching parents: emotional support, information exchange and a structured process of tutoring parenting behaviours	Augmented effects of BoNT (BS)  Reduced muscle spasticity (BS)	Graham <sup>82</sup>  Katalinic <sup>79</sup> Teplicky <sup>82</sup>	Insufficient evidence. More research needed with stronger designs  Insufficient evidence. Newer understandings of spasticity indicate a 'local' intervention will not improve a 'central' condition – therefore probably do not use casting for spasticity reduction	4  1 1	Very low  Low Low	Weak +  Weak – Weak –	Yellow MEASURE  Yellow MEASURE Yellow MEASURE
15 Cognitive behaviour therapy (CBT): identifying unhelpful thoughts and behaviours and teaching cognitive restructuring and self-management of constructive thinking and actions	Improved parenting skills and coping (E)  Improved depression, anxiety, sleep, attention, behaviour and enuresis (BS)	–  Graham <sup>82</sup>	No evidence in CP. Since high-quality evidence supports CBT in non-CP populations – therefore probably do use CBT	–	N/A	Weak +	Yellow MEASURE
16 Communication training: training communication partners to effectively communicate, e.g. Interaction Training; Hanen; It Takes Two to Talk	Improved interaction between children and their parents (P)	Pennington <sup>29</sup> Pennington <sup>83</sup>	Insufficient evidence	1 1	Very low	Weak +	Yellow MEASURE
17 Conductive education (CE): a Hungarian educational classroom-based approach to teaching movement using rhythmic intention, routines and groups	Improved 'orthofunction' (response to biological and social demands) (BS)  Improved performance of functional activities (A)  Improved cognition (BS)	Darrah <sup>84</sup> Tuersley-Dixon <sup>85</sup>  Darrah <sup>84</sup> Tuersley-Dixon <sup>85</sup>  Dixon <sup>85</sup>	Conflicting evidence. Majority of studies show no difference to no treatment  Conflicting evidence. Majority of studies show no difference to no treatment  Conflicting evidence. Majority of studies show no difference to no treatment	1 1  1 1  1	Low  Low  Low  Low	Weak –  Weak –  Weak –  Weak –	Yellow MEASURE  Yellow MEASURE  Yellow MEASURE  Yellow MEASURE
18 Constraint-induced movement therapy (CIMT): constraining the dominant hand in a mitt or cast, to enable intensive training of the hemiplegic hand	Improved hand function of the affected hand for children with hemiplegia (A)	Hoare <sup>86</sup> Huang <sup>87</sup>  Nascimento <sup>88</sup> Sakzewski <sup>4</sup> Law <sup>25</sup>	Effective. Even more RCTs have been published after the included reviews confirming effectiveness	1 1  1 1 1	Moderate  Low  Low  Low	Strong +  Strong +  Weak –  Weak –	Green GO  Green GO  Yellow MEASURE Yellow MEASURE
19 Context-focused therapy: changing the task or the environment (but not the child) to promote successful task performance	Improved function (A)	–	Effective. Note: a single rigorous RCT shows equal effectiveness to child-focused therapy	2	High	Strong +	Green GO
20 Counselling (parents): fostering understanding of how life problems lead to distress, relationship breakdown and mental health issues, to improve communication and interpersonal skills	Improved parental coping and mental health (E) Improved parental coping via parent to parent support (E)	Palit <sup>90</sup>	No evidence in CP. No published research evidence, opinion papers existed Insufficient evidence	– 4	N/A Very low	Weak + Weak +	Yellow MEASURE Yellow MEASURE



Table 1: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	GRADE		
				Oxford evidence level	Quality of evidence	Strength of recommendation
21	Cranial osteopathy: palpation using small movements to ease musculoskeletal strain and treat the central nervous system	Wyatt <sup>91</sup>	Ineffective. Note: a single rigorous RCT shows no benefit when compared to no treatment	2	High	Strong –
22	Dantrolene: antispasticity medication	Delgado <sup>26</sup>	Insufficient evidence	1	Low	Weak –
23	Diazepam: antispasticity medication	Delgado <sup>26</sup>	Effective short term, therefore – do use	1	Moderate	Strong +
24	Dysphagia management: promoting safe swallowing by changing food textures, sitting position, oral motor skills and using oral appliances and equipment	Snider <sup>92</sup>	Lower-quality supporting evidence	1	Low	Weak +
25	Early intervention (EI): therapy and early education to promote acquisition of milestones, via group or individual stimulus	Snider <sup>92</sup>	Conflicting evidence	1	Low	Weak +
		Blauw-Hospers <sup>93</sup>	Evidence supports general stimulation, developmental approaches and parent coaching programmes. Gains are superior to NDT or traditional physiotherapy	1	Moderate	Weak +
		Blauw-Hospers <sup>94</sup>		1		
		Turnbull <sup>95</sup>		1		
		Ziviani <sup>96</sup>		1		
		Blauw-Hospers <sup>93</sup>		1		
		Blauw-Hospers <sup>94</sup>		1		
		Turnbull <sup>95</sup>		1		
26	Electrical stimulation (ES, NMES, FES): electrical stimulation of a muscle through a skin electrode to induce passive muscle contractions for strengthening or motor activation	Cauraugh <sup>97</sup> Wright <sup>97</sup> Kerr <sup>98</sup> Scianni <sup>99</sup> Wright <sup>97</sup> Lannin <sup>100</sup> Wright <sup>101</sup> Butler <sup>102</sup> Rogers <sup>103</sup> Verschuren <sup>102</sup>	High quality evidence supports EI in non-CP populations. Moderate evidence supports EI program memes for at risk pre-term infants, aimed at mimicking the intrauterine environment	1	Low	Weak +
		Ziviani <sup>96</sup>		1		
		Cauraugh <sup>97</sup>		1		
		Wright <sup>97</sup>		1		
		Kerr <sup>98</sup>		1		
		Scianni <sup>99</sup>		1		
		Wright <sup>97</sup>		1		
		Lannin <sup>100</sup>		1		
		Wright <sup>101</sup>		1		
		Butler <sup>102</sup>		1		
		Rogers <sup>103</sup>		1		
27	Fitness training: planned structured activities involving repeated movement of skeletal muscles that result in energy expenditure to improve or maintain levels of physical fitness	Butler <sup>102</sup> Rogers <sup>103</sup> Verschuren <sup>102</sup>	Insufficient evidence. Effective in laboratory, unknown effectiveness in the community	1	Low	Weak +
		Butler <sup>102</sup>	Lower-quality supporting evidence	1		
		Rogers <sup>103</sup>		1		
		Verschuren <sup>102</sup>		1		
		Butler <sup>102</sup>	Conflicting evidence. More evidence needed	1	Low	Weak +
		Rogers <sup>103</sup>		1		
		Verschuren <sup>102</sup>		1		
28	Fundoplication (including Nissen and laparoscopic; gastric plication): surgical procedure to strengthen the barrier to acid reflux, e.g. by wrapping the fundus around the oesophagus	Butler <sup>102</sup> Rogers <sup>103</sup> Vernon <sup>103</sup> Roberts <sup>103</sup>	Effective short term and only in those that have sufficient motor skills to undertake aerobic training. No carryover when training stops. Therefore do use but only in the right patient and plan to continue the programme long term	1	Moderate	Strong +
		Butler <sup>102</sup>	Insufficient evidence. Aerobic fitness does not appear to translate to activity and participation gains	1		
		Rogers <sup>103</sup>		1		
		Vernon <sup>103</sup>		1		
		Roberts <sup>103</sup>	No CP-specific evidence	1	N/A	Weak +

**Table 1:** Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	GRADE		
				Oxford evidence level	Quality of evidence	Strength of recommendation
29	Gastrostomy: surgical placement of a non-oral feeding tube to prevent or reverse growth failure, or prevent aspiration pneumonia, e.g. percutaneous endoscopic gastrostomy (PEG), jejunostomy	Arrowsmith <sup>104</sup>	Adverse events occur	3	Very low	Weak +
		Kong <sup>105</sup>		3		
		Samson-Fang <sup>106</sup>		1		
		Sleigh <sup>107,108</sup>		1		
30	Goal-directed training/functional training: task specific practice of child-set goal-based activities using a motor learning approach	Sullivan <sup>109</sup>	Effective. Some probability of bias within included studies	3	Low	Weak +
		Sullivan <sup>110</sup>		3		
		Vernon-Roberts <sup>111</sup>		4		
		Ketelaar <sup>112</sup>		2		
31	Hand surgery: surgery to improve hand function and alignment	Loving <sup>113</sup>	Effective. Can be delivered via a home programme or used in combination with CIMT and bimanual training. Low probability of bias within included studies	3	High	Strong +
		Novak <sup>13</sup>		2		
		Sakzewski <sup>52</sup>		2		
		Wallen <sup>14</sup>		2		
32	Hip surgery: orthopaedic surgery to improve musculoskeletal alignment of the hip	Novak <sup>13</sup>	Effective. Low probability of bias within included studies	2	High	Strong +
		Wallen <sup>14</sup>		2		
		Smeulders <sup>114</sup>		1		
		Stott <sup>115</sup>		1		
33	Hip surveillance: active surveillance and treatment for hip joint integrity to prevent hip dislocation	Brunner <sup>116</sup>	Studies were retrospective and uncontrolled	4	Very low	Weak +
		Huh <sup>117</sup>		4		
		Gordon <sup>118</sup>		1		
34	Hippotherapy: therapeutic horse riding to practice balance and symmetry		Hip surveillance is a regular assessment process so as the right treatments can be provided in a timely manner, as such the studies were appropriately designed as observational studies not RCTs. Do use as there are substantive adverse events from no surveillance		Moderate	Strong +
		Snider <sup>119</sup>				
		Sterba <sup>120</sup>				
		Zadnikar <sup>121</sup>				
35	Home programmes: therapeutic practice of goal-based tasks by the child, led by the parent and supported by the therapist, in the home environment	Whalen <sup>122</sup>	Effective. Larger studies needed	1	Low	Weak +
36	Hydrotherapy: aquatic-based exercises	Davis <sup>123</sup>	Insufficient evidence. Sensitive measures required in future studies	2	Moderate	Weak –
37	Hyperbaric oxygen (HBO): inhaled 100% oxygen inside a pressurized hyperbaric chamber	Novak <sup>124</sup>	Effective. Note: a single rigorous RCT shows effectiveness, with a low probability of bias	1	Moderate	Strong +
		Novak <sup>13</sup>		2		
		Novak <sup>13</sup>		2		
38	Hydrotherapy: aquatic-based exercises	Chrysagis <sup>125</sup>	Lower-quality supporting evidence	2	Low	Weak +
		Getz <sup>126</sup>		1		
		Gorter <sup>127</sup>		1		
		Collet <sup>128</sup>		2		
39	Hyperbaric oxygen (HBO): inhaled 100% oxygen inside a pressurized hyperbaric chamber	McDonagh <sup>129</sup>	Ineffective. Adverse events can also occur	1	High	Strong –

Table 1: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	GRADE		
				Oxford evidence level	Quality of evidence	Strength of recommendation
38 Intrathecal baclofen (ITB): antispasticity medication delivered directly to the spinal cord via a pump surgically implanted within the abdomen	Reduced lower limb spasticity (BS)	Butler <sup>130</sup> Creedon <sup>131</sup> Dan <sup>132</sup> Delgado <sup>26</sup> Kolaski <sup>133</sup>	Predominantly low-quality supporting evidence. The size of the gains varies between studies	1	Low	Weak +
	Reduced upper limb spasticity (BS)	Butler <sup>130</sup> Creedon <sup>131</sup> Dan <sup>132</sup> Delgado <sup>26</sup> Kolaski <sup>133</sup>	Insufficient evidence. The effect on upper limb is less than for the lower limb and some authors question whether ITB is clinically worthwhile for the purposes of reducing upper limb spasticity	1	Low	Weak –
	Reduced dystonia (BS)	Albanese <sup>134</sup> Butler <sup>130</sup>	Lower-quality supporting evidence	1	Very low	Weak +
	Improved function and health related quality of life (A, P and PF)	Hoving <sup>135</sup> Hoving <sup>136</sup> Kolaski <sup>133</sup>	Lower-quality supporting evidence	2	Low	Weak +
	Improved walking ability in ambulant children (A)	Kolaski <sup>133</sup> Pin <sup>137</sup>	Insufficient evidence. Some children with CP improve but many experience adverse events including inability to walk	1	Very low	Weak –
	Reduced pain (BS)	Hernandez-Reif <sup>138</sup> Nilsson <sup>139</sup>	Conflicting evidence	2	Low	Weak +
	Reduced spasticity (BS)	Alizadeh <sup>140</sup> Hernandez-Reif <sup>138</sup>	Conflicting evidence	2	Low	Weak +
	Improved function (A)	Hernandez-Reif <sup>138</sup>	Conflicting evidence	2	Low	Weak +
	Normalized movement (BS)	Brown <sup>141</sup> Butler <sup>142</sup>	Ineffective. No gains superior to other treatments	1	Low	Strong –
	Prevent contracture development (BS)	Brown <sup>141</sup> Butler <sup>142</sup>	Ineffective because immediate gains in range of motion observed within the session do not carry over	1	Low	Strong –
	Improved function (A)	Brown <sup>141</sup> Butler <sup>142</sup> Martin <sup>143</sup>	Conflicting systematic review evidence. Early reviews suggested no benefits. The more recent review included one new trial suggesting possible benefit of higher doses of NDT compared with lower doses of NDT; however, this is not a conventional method for establishing treatment efficacy and should be interpreted with caution. Other evidence shows that motor learning produces superior functional gains to NDT	1	Low	Weak –
	Enhanced social emotional and cognitive skills (BS and PF)	Brown <sup>141</sup> Butler <sup>142</sup>	Ineffective. No evidence to support claim	1	Low	Strong –
	Improved goal achievement of upper limb activities (A)	Boyd <sup>69</sup> Fehlings <sup>65</sup> Hoare <sup>70</sup> Hoare <sup>71</sup> Lannin <sup>99</sup>	Effective	1	High	Strong +
41 Occupational therapy after BoNT: improved hand use via CIMT, goal-directed training, strength training and functional hand splints. improved symptom management via casting and immobilisation splints						Red STOP Green GO

Table 1: Continued

Intervention	GRADE	Oxford evidence level	Quality of evidence	Strength of recommendation	Traffic light action
42 Oral motor treatment: sensory stimulation to lips, jaw, tongue, soft palate, larynx, and respiratory muscles to influence the oropharyngeal mechanism		–	N/A	Weak –	Yellow MEASURE
43 Orthopaedic surgery: surgical prevention or correction of musculoskeletal disorders and associated muscles, joints, and ligaments, e.g. muscle lengthening		Snider <sup>92</sup>	1	Weak –	Yellow MEASURE
		Wilcox <sup>144</sup>	1	Weak +	Yellow MEASURE
		Shore <sup>145</sup>	1	Weak +	Yellow MEASURE
44 Orthotics (splints): removable external devices designed to support weak or ineffective joints or muscles		Auti-Ramo <sup>76</sup>	1	Weak +	Yellow MEASURE
		Blackmore <sup>77</sup>	1	Weak +	Yellow MEASURE
45 Parent training: educating and coaching parents to change their child's behaviour or skills, plus improve parenting		Effgen <sup>78</sup>	1	Weak –	Yellow MEASURE
		Harris <sup>147</sup>	1	Weak –	Yellow MEASURE
		Morris <sup>148</sup>	1	Weak –	Yellow MEASURE
		Teplicky <sup>81</sup>	1	Weak –	Yellow MEASURE
		Teplicky <sup>81</sup>	1	Weak –	Yellow MEASURE
		Teplicky <sup>81</sup>	1	Weak –	Yellow MEASURE
		Teplicky <sup>81</sup>	1	Weak –	Yellow MEASURE
		Teplicky <sup>81</sup>	1	Weak –	Yellow MEASURE
		Teplicky <sup>81</sup>	1	Weak –	Yellow MEASURE
		Teplicky <sup>81</sup>	1	Weak –	Yellow MEASURE
46 Phenol: muscular injections to induce chemical denervation for treating local spasticity		Graham <sup>149</sup>	2	Strong –	Red STOP
		Whittingham <sup>50</sup>	1	Weak +	Yellow MEASURE
47 Play therapy: play and creative arts to enhance emotional wellbeing and advance play skills		Delgado <sup>26</sup>	1	Weak –	Yellow MEASURE
		Redditi <sup>150</sup>	2	Weak +	Yellow MEASURE
48 Pressure care: prevention of pressure ulcers via good positioning, repositioning, and suitable support surfaces		Hanzlik <sup>150</sup>	–	Weak +	Yellow MEASURE
		McInnes <sup>151</sup>	1	Strong +	Green GO
49 Wheelchair cushions: pressure redistributing, pressure relieving, and pressure supporting		McInnes <sup>151</sup>	1	Weak +	Yellow MEASURE
		McInnes <sup>151</sup>	1	Weak +	Yellow MEASURE

Table 1: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE		Traffic light action
					Quality of evidence	Strength of recommendation	
49	Respite: temporary caregiving break for parents where the child is usually accommodated outside the home	Strunk <sup>152</sup>	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
50	Seating and positioning: assistive technology that enables a person to sit upright with functional, symmetrical or comfortable posture, to enable function	Farley <sup>153</sup>	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
		Ryan <sup>154</sup>					
		Chung <sup>155</sup>					
		Farley <sup>153</sup>					
		Roxborough <sup>156</sup>					
51	Selective dorsal rhizotomy (SDR): neurosurgical procedure that selectively severs nerve roots in the spinal cord, to relieve spasticity	Ryan <sup>154</sup>	Lower-quality supporting evidence	1	Very low	Weak +	Yellow MEASURE
		Farley <sup>153</sup>					
		McNamara <sup>157</sup>					
		Ryan <sup>154</sup>					
		Michael <sup>158</sup>					
52	Sensory integration (SI): therapeutic activities to organize sensation from the body and environment, to facilitate adaptive responses, e.g. hammock swinging	Grun <sup>159</sup>	Effective	1	Moderate	Strong +	Yellow MEASURE Green GO
		McLaughlin <sup>160</sup>					
		Steinbok <sup>161</sup>					
		Grun <sup>159</sup>					
		McLaughlin <sup>160</sup>					
53	Sensory processing: therapeutic activities to organize more appropriate responsiveness (i.e. not hyper-responsive and not hyporesponsive) to task and environmental demands, including self-regulation	Steinbok <sup>161</sup>	Effective	1	Low	Strong +	Green GO
		Grun <sup>159</sup>					
		McLaughlin <sup>160</sup>					
		Steinbok <sup>161</sup>					
		Vargas <sup>162</sup>					
54	Single event multilevel surgery with therapy: multiple simultaneous surgical procedures at different levels of the lower limb to either improve gait or prevent deterioration	Vargas <sup>162</sup>	Evidence for improved gross motor function, but no supporting evidence for general activities and participation and this should not be the primary goal for using SDR	1	Very low	Weak +	Yellow MEASURE
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
55	Social stories: an individualized book describing a situation, skill, or concept and the relevant social cues, perspectives, and common responses to prepare a child for a social situation	Vargas <sup>162</sup>	Ineffective. Since meta-analyses of SI compared with no treatment had average effect sizes of 0.03 (for most recent studies), and 0.09 for SI compared to alternative treatments. Note reviews for non-CP populations excluded	1	Low	Strong –	Red STOP
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
56	Solution-focused brief therapy: resource orientated and goal focused approach to generating solutions to life challenges	Vargas <sup>162</sup>	No evidence in CP. Since performance-based approaches (e.g. CO-OP) are more favourable than impairment-based approaches, e.g. sensory processing (in non-CP populations)	1	N/A	Weak –	Yellow MEASURE
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
56	Solution-focused brief therapy: resource orientated and goal focused approach to generating solutions to life challenges	Vargas <sup>162</sup>	No evidence in CP. Since low-quality evidence shows emergent effectiveness in non-CP populations <sup>158</sup>	1	Very low	Weak +	Yellow MEASURE
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					
		Vargas <sup>162</sup>					

Table 1: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	Oxford evidence level	GRADE		
					Quality of evidence	Strength of recommendation	Traffic light action
57	Strength training (resistance): use of progressively more challenging resistance to muscular contraction to build muscle strength and anaerobic endurance	Dodd <sup>165</sup> Effen <sup>78</sup> Jeglinsky <sup>166</sup> Martin <sup>143</sup> Mockford <sup>167</sup> Scianni <sup>168</sup> Taylor <sup>169</sup> Kim <sup>170</sup>	Effective short term for improving muscle strength. Improved muscle strength does not carry over to function, other treatment approaches will be needed for functional gains	1 1 1 1 1 1 1 2	Low	Weak +	Yellow MEASURE
	Improved upper limb strength via progressive resistance training (BS)		Effective short term for improving muscle strength		Low	Weak +	Yellow MEASURE
	Improved function via progressive resistance training (A)	Scianni <sup>168</sup>	Insufficient evidence	1	Low	Weak –	Yellow MEASURE
	Improved function via functional training using resistance within functional tasks (A)	Martin <sup>143</sup>	Lower-quality supporting evidence	1	Low	Weak +	Yellow MEASURE
58	Stretching: use of an external passive force (e.g. parent) exerted upon the limb to move it into a new and lengthened position	Katalinic <sup>79</sup> Wiaar <sup>171</sup>	Ineffective. Comprehensive and robust meta-analysis showed no immediate, or short- to medium-term benefits (<7mo), but, since only a small number of CP studies were included within the review, it is not possible to be certain about this recommendation for CP	1 1	Moderate	Weak –	Yellow MEASURE
	Contracture prevention via splinting or positioning (BS)	Autti-Ramo <sup>76</sup> Pin <sup>45</sup>	Insufficient evidence	1 1	Low	Weak +	Yellow MEASURE
59	Therasuits: a breathable soft dynamic orthotic full body suit, designed to improve proprioception, reduce reflexes, restore synergies and provide resistance	Teplicky <sup>81</sup> Alagesan <sup>172</sup> Bailes <sup>173</sup>	Conflicting evidence. One trial suggests positive effect the other suggest no benefits	2 2	Low	Weak –	Yellow MEASURE
60	Tizanidine: antispasticity medication	Delgado <sup>26</sup>	Insufficient evidence	1	Low	Weak +	Yellow MEASURE
61	Treadmill training: walking practice on a treadmill, which includes partial body support	Zwicker <sup>174</sup> Damiano <sup>175</sup> Mutlu <sup>176</sup> Willoughby <sup>177</sup> Zwicker <sup>174</sup> Fehlings <sup>55</sup> Hough <sup>56</sup>	Lower-quality supporting evidence	1 1 1 1 1 1 1	Low	Weak +	Yellow MEASURE
62	Vitamin D (with or without calcium or growth hormones): dietary vitamin supplement for bone density		Insufficient evidence	1	Low	Weak +	Yellow MEASURE
63	Vojta: therapist applied pressure to defined zones on the body whilst positioned in prone, supine or side lying, where the stimulus leads to automatically and involuntarily complex movement	Brandt <sup>178</sup> d'Avignon <sup>179</sup> Kanda <sup>180</sup> Liu <sup>181</sup> Wu <sup>182</sup> Zhang <sup>183</sup> Zhao <sup>188</sup>	Conflicting evidence. Studies claim to 'cure' early CP, which is not consistent with any of the other literature about CP having no known cure. Also the studies reported high dropout rates due to child distress. Studies have a high probability of bias, e.g. lack of: random sequence generation; concealed allocation, study blinding, psychometrically sound instruments; plus incomplete outcome data collection and selective reporting	2 2 3 2 2 2 2	Very low	Weak –	Yellow MEASURE

Table I: Continued

Intervention	Intervention outcome (ICF level)	Citations	Panel comments	GRADE			
				Oxford evidence level	Quality of evidence	Strength of recommendation	Traffic light action
64 Whole-body vibration: assistive technology that transmits low-frequency vibration to the body through a broad contact area of a vibrating surface, e.g. feet in standing, buttocks in sitting, or whole body	Improved strength (BS)	del Pozo-Cruz <sup>185</sup>	Lower-quality supporting evidence in non-CP population, but no effect in CP. Small numbers of CP studies we cannot be certain about this recommendation for CP	1	Very low	Weak –	Yellow MEASURE
	Improved gait (BS and A)	del Pozo-Cruz <sup>185</sup>	Insufficient evidence	1	Very low	Weak –	Yellow MEASURE

Under 'Quality of evidence', 'High' means that further research is very unlikely to change our confidence in the estimate of effect; 'Moderate' means that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; 'Low' means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and 'Very low' means that any estimate of effect is very uncertain.<sup>17</sup> Under 'Strength of recommendation', 'Strong +' means 'do it', indicating a judgement that most well-informed people would make; 'Weak +' means 'probably do it', indicating a judgement that a majority of well-informed people would make but a substantial minority would not; 'Weak –' means 'probably do not do it', indicating a judgement that a majority of well-informed people would make but a substantial minority would not; 'Strong –' means 'do not do it', indicating a judgement that most well-informed people would make.<sup>17</sup> A, activities; BS, body structures and function; P, participation; RCT, randomized controlled trial; E, environmental; PF, personal factors.

using the Oxford Levels of Evidence; a categorization using GRADE; a colour coding scheme using the Evidence Alert Traffic Light system, and an ICF domain (Table I). More specifically, each intervention outcome sought by included study authors was assigned an ICF domain based upon published literature.<sup>176</sup> It has been acknowledged in the literature that ICF coding is notoriously complex to apply since CP is a disability not a disease, and thus direct interventions do not ultimately alter underlying disease processes.<sup>10</sup> To overcome this challenge, we applied ICF codes using CP literature precedents, where the outcome measure within the included trials had been ICF coded by other authoritative researchers.<sup>10</sup> Of note, ICF linking rules typically cluster together (1) body structure and functions; and (2) activities and participation. To prevent loss of findings obscured within aggregated data, we separated activities from participation because we wanted to illuminate whether or not participation outcomes were being achieved. All the data required to answer the study questions were published within the papers, so no contact with authors was necessary.

### Ethics and registration

The study did not involve contact with people, so the need for ethical approval was waived by the Cerebral Palsy Alliance's Human Research ethics committee. This systematic review was not registered.

### RESULTS

Using the search strategy, 33 485 citations were identified, of which 166 articles met the inclusion criteria for review (Fig. 2).

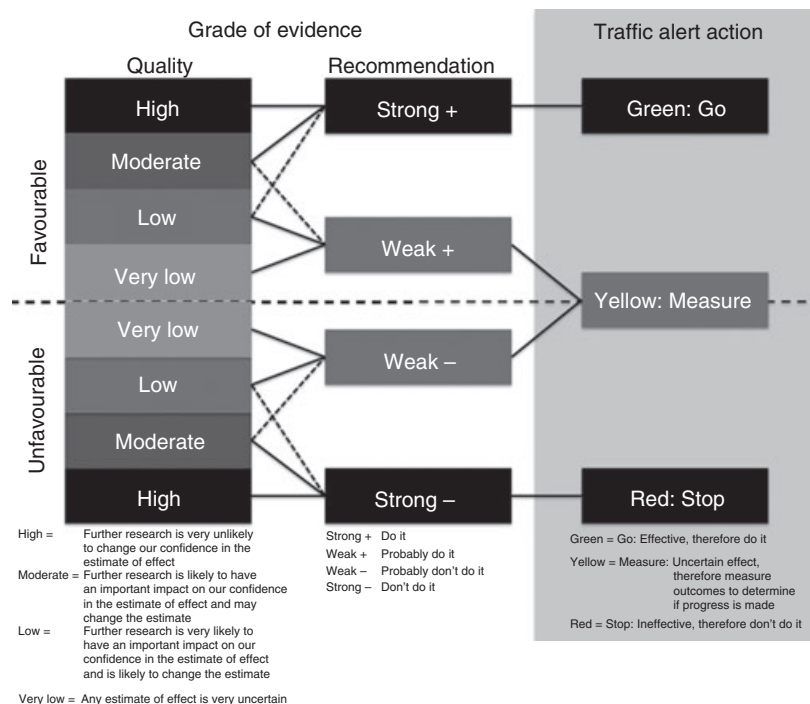
### Participants

For the purpose of this study, participants had CP, which is a complex and heterogeneous condition. We included studies about children with CP of any motor subtype (spastic, dyskinetic, or ataxic), any topography (hemiplegic/unilateral, diplegic/bilateral, or quadriplegic/bilateral), and any functional ability level (Gross Motor Function Classification System [GMFCS]<sup>188</sup> levels I to V and Manual Ability Classification System [MACS]<sup>189</sup> levels I to V). There was substantial emphasis in the medical literature on interventions to reduce spasticity, the most prevalent motor impairment.<sup>190</sup> There was also a heavy emphasis in the therapy literature on interventions designed to improve motor outcomes consistent with CP being a physical disability. The higher-quality studies defined the child's motor function abilities using the GMFCS and MACS to enable better interpretation of treatment effects taking into account the severity of the disability. However, there was insufficient homogeneity of reporting across studies to enable reporting by GMFCS level, which was our original intended strategy.

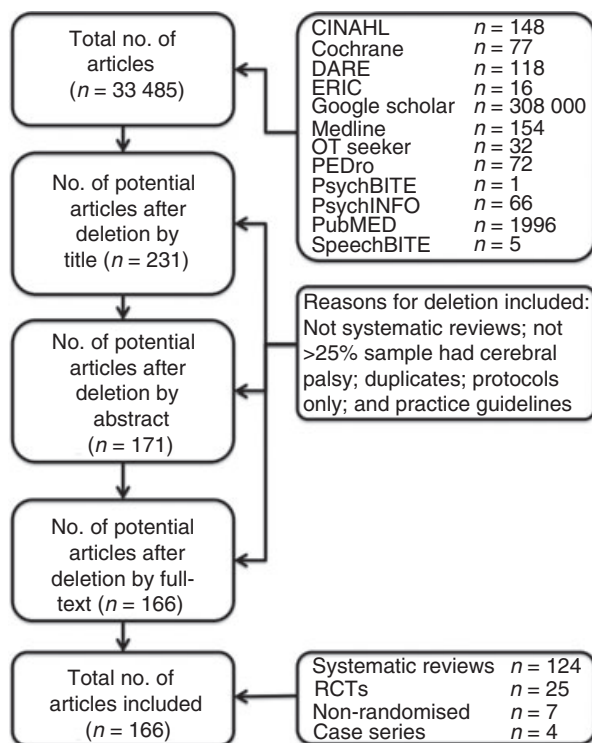
### Levels of evidence and ICF

High levels of evidence existed in the literature summarizing interventions for children with CP (Table I). Of the





**Figure 1:** Relationship between the GRADE and Traffic Light System.



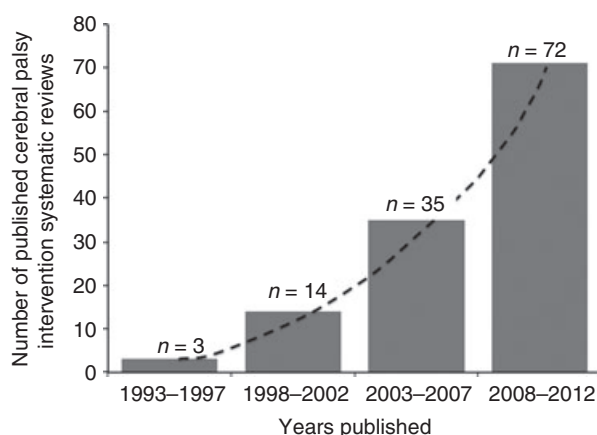
**Figure 2:** Flow diagram of included articles.

166 included studies, the breakdown by level of evidence as rated on the Oxford Levels of Evidence was level 1 ( $n=124$ ), 74%; level 2 ( $n=30$ ), 18%; level 3 ( $n=6$ ), 4%; and level 4 ( $n=6$ ), 4%.

When the included articles were tallied in 5-year intervals by publication date, it was clear that the number of systematic reviews published about CP intervention had exponentially increased in recent years (Fig. 3).

Almost none (2 of 166) of the systematic reviews retrieved graded the body of evidence summarized using the GRADE system. We therefore carried out assignment of GRADEs using the recommended expert panel methodology. Using the GRADE system, of the 64 different CP interventions reviewed across 131 intervention outcomes 16% of outcomes assessed ( $n=21$ ) were graded 'do it' (i.e. green light, go interventions); 58% ( $n=76$ ) were graded 'probably do it' (i.e. yellow light, measure outcomes); 20% ( $n=26$ ) were graded 'probably do not do it' (i.e. yellow light, measure outcomes; see Fig. 1); and 6% ( $n=8$ ) were graded 'do not do it' (i.e. red light, stop interventions; see Fig. 1). In line with the appraisal criteria for this review, occupational therapy, physiotherapy, and medicine were the disciplines that encompassed the highest number of proven effective interventions for CP within their evidence base, which is not surprising given the long historical research emphasis on redressing the physical aspects of CP. In the fields of psychology, speech pathology, social work, and education, the evidence base for all interventions reviewed was lower level or inconclusive (yellow), but, in keeping with interdisciplinary care, psychologists and social





**Figure 3:** Number of published cerebral palsy intervention systematic reviews.

workers applied high-level evidence from other diagnostic groups (e.g. bimanual, cognitive behaviour therapy, counselling, Triple P<sup>49</sup>). In the field of speech pathology, it is worth noting that it is difficult to conduct studies of augmentative and alternative communication (AAC) using conventional rigorous methodologies because included participants often have different disability types and, accordingly, differing levels of expressive, receptive, and social communication abilities. AAC interventions require multifactorial measurement because effective device utilization relies on changes in all of these domains from best-practice speech, language, and teaching strategies and from changing the mode of communication. Thus, adequately measuring and attributing interventions effects to each component of these integrated treatment approaches remains challenging. Amongst the alternative and complementary medicine interventions offered by some clinicians, the findings were of even poorer quality, because an even greater proportion of the interventions were proven ineffective. However, the real rate of ineffective alternative and complementary interventions may be even higher as so many had to be excluded from this review as a result of the lack of any published peer-reviewed literature about the approaches (e.g. advanced biomechanical rehabilitation).

Each intervention was coded using the ICF by the intervention's desired outcome. Out of the 131 intervention outcomes for children with CP identified in this study,  $n=66$  (51%) were aimed at the body structures and function level;  $n=39$  (30%) were aimed at the activity level;  $n=7$  (5%) were aimed at the participation level;  $n=8$  (6%) were aimed at the environment level; and the remaining  $n=11$  (8%) were aimed at combinations of ICF levels.

### Green light go interventions

In the papers retrieved, the following CP interventions were shown to be effective: (1) botulinum toxin (BoNT), diazepam, and selective dorsal rhizotomy for reducing muscle spasticity; (2) casting for improving and maintain-

ing ankle range of motion; (3) hip surveillance for maintaining hip joint integrity; (4) constraint-induced movement therapy, bimanual training, context-focused therapy, goal-directed/functional training, occupational therapy following BoNT, and home programmes for improving motor activity performance and/or self-care; (5) fitness training for improving fitness; (6) bisphosphonates for improving bone density; (7) pressure care for reducing the risk of pressure ulcers; and (8) anticonvulsants for managing seizures (despite no CP-specific anticonvulsant evidence existing, the panel rated the strength of the recommendation as strong plus (do it) because good-quality evidence supports anticonvulsants in non-CP populations,<sup>191</sup> and serious harm, even death, can arise from no treatment).

Green light effective interventions were mapped against the ICF by the outcomes that had been measured in the literature and the corresponding traffic light code was applied (Table II). First, Table II shows that green-light effective interventions were all aimed at either the body structures and function level or the activities levels on the ICF. The conspicuous finding here was that there were no proven effective interventions for addressing the participation, environment, or personal factors levels of the ICF, even though these are philosophical priorities. Second, Table II shows that when effective body structures and functions interventions were measured for an effect at the activities level (all of the time) evidence of effect was either lower level or inconclusive and, therefore, was coded yellow light. In other words, the positive effects of body structure interventions did not translate 'upstream' to the activities level. This finding seems to suggest that you 'get what you give'. This finding has, however, an alternative interpretation – we do not yet know if body structures and functions intervention improves outcomes at the activities level because of the measurement artefact created by randomized trials only being powered to detect change in one primary end-point. Third, Table II shows that green light activity-level interventions were effective at the activities level of the ICF, but minimal measurement had been undertaken to illuminate whether or not there was also any translation of impact 'downstream' to the body structures and functions level.

### Yellow light measure outcomes interventions

A high proportion (70%) of the CP interventions within clinical care had either lower-level evidence supporting their effectiveness or inconclusive evidence, including acupuncture; alcohol (intramuscular injections for spasticity reduction); AAC; animal-assisted therapy; assistive technology; baclofen (oral); behaviour therapy and coaching; cognitive behaviour therapy; communication training; conductive education; counselling; oral dantrolene; dysphagia management; early intervention (for motor outcomes); electrical stimulation; fundoplication; gastrostomy; hand surgery; hip surgery; hippotherapy; hydrotherapy; intrathecal baclofen; massage; orthoses; oral-motor

**Table II:** Green light interventions (and their other indications) by level of ICF

Intervention	ICF level				
	Body structures and function	Activity	Participation	Environment	Personal factors
<b>Body structures and function interventions</b>					
1. Anticonvulsants	G				
2. Botulinum toxin	G				
3. Bisphosphonates	G				
4. Casting (ankle)	G	Y			
5. Diazepam	G				
6. Fitness training	G	Y	Y		
7. Hip surveillance	G				
8. Pressure care	G				
9. Selective dorsal rhizotomy	G	Y	Y		
<b>Activities interventions</b>					
10. Bimanual training		G			
11. Constraint-induced movement therapy		G			
12. Context-focused therapy		G			
13. Goal-directed training/functional training		G			
14. Home programmes		G	Y		
15. Occupational therapy post botulinum toxin (upper limb)		G			

G=green intervention when aimed at this level of the International Classification of Functioning, Disability and Health (ICF); Y=yellow intervention when aimed at this level of the ICF.

therapy; orthopaedic surgery; parent training; phenol (intramuscular injections); play therapy; respite; seating and positioning; sensory processing; single-event multilevel surgery; social stories; solution-focused brief therapy; strength training; stretching; therasuits; oral tizanidine; treadmill training; oral vitamin D; Vojta; and whole-body vibration. It is important to note that cognitive-behavioural therapy,<sup>192–196</sup> early intervention,<sup>196–198</sup> parent training,<sup>49,50</sup> and solution-focused brief therapy<sup>199</sup> all have good-quality supporting evidence in non-CP populations. It is also important to note that oral-motor therapy<sup>200</sup> and sensory processing<sup>201</sup> have equivocal evidence in non-CP populations for which they were designed, and so there is no strong or compelling reason to think either intervention would work better in CP. Of note, there was great variability in the volume and quality of the evidence available at the yellow-light level. For example, some intervention evidence bases were downgraded to low quality, as per the GRADE guidelines for dealing with imperfect randomized controlled trials (e.g. hippotherapy and biofeedback). However, for some interventions simply next to no evidence has been published and what has been published involves very small numbers and is of low quality (e.g. whole-body vibration).

The yellow-light included reviews that could not demonstrate robust evidence of effectiveness when strict systematic review criteria about design quality, adequate sample size, and independent replication were used to judge the evidence. Yellow-light reviews contained only marginal amounts of good-quality evidence when criteria were applied to reduce the possibility of biases explaining the proposed treatment benefits. Most yellow-light systematic review authors commented upon the low quality of the

designs used, serious methodological flaws, the relevance and sensitivity of the outcomes measures adopted, the difficulty in assembling large homogeneous samples for niche interventions, and most authors concluded that more rigorous research was needed.

### Red light stop interventions

Craniosacral therapy, hip bracing, hyperbaric oxygen, NDT, and sensory integration have all been shown to be ineffective in children with CP, and are therefore not recommended for standard care. Appropriately, effective alternatives exist that seek to provide the same clinical outcome of interest.

To assist with comparative clinical decision-making amongst intervention options for the same desired outcome, we mapped the interventions that seek to provide analogous outcomes using bubble charts. In the bubble charts, the size of the circle correlated to the volume of published evidence. The circle size was calculated using (1) the number of published papers on the topic; and (2) the total score for the level of evidence (calculated by reverse coding of the Oxford Levels of Evidence, i.e. expert opinion=1, randomized controlled trial [RCT]=5). The location of the circle on the y-axis of the graph corresponds to the GRADE system rating. The colour of the circle correlates to the Evidence Alert System (Fig. 4).

### DISCUSSION

High levels of evidence existed in the literature summarizing intervention options for children with CP. Akin to other fields of medicine and allied health, there has been an exponential increase in the number of systematic reviews published about CP intervention<sup>6</sup> revealing the emergence of



**Figure 4:** State of the evidence for cerebral palsy intervention by outcomes.

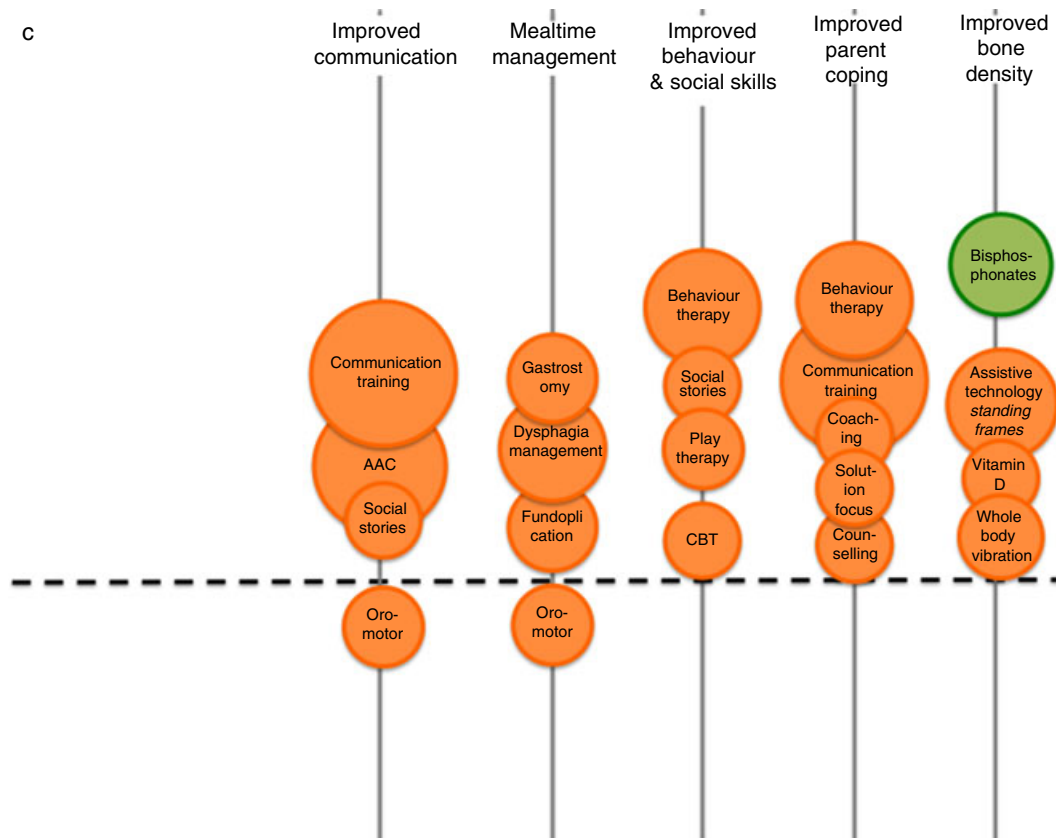


Figure 4: Continued.

highly effective prevention interventions.<sup>186,187</sup> There is no reason to think that this trend may decline. This finding has important implications for managers, knowledge brokers, and clinicians about finding effective and efficient ways for health professionals to remain up to date with the latest practice. Best available knowledge translation evidence suggests that managers and senior clinical mentors can help staff maintain up-to-date knowledge via interactive evidence-based practice continuing education sessions and journal clubs, but multiple tailored strategies will be required to change their use of evidence.<sup>202</sup> This systematic review could form the basis of policy, educational, and knowledge translation material because it is a comprehensive summary of the evidence base.

### Recommendations for practice

Based upon the best available evidence, standard care for children with CP should include the following suite of interventions options (where the interventions would address the family's goals): (1) casting for improving ankle range of motion for weight bearing and/or walking; (2) hip surveillance for maintaining hip joint integrity; (3) bimanual training, constraint-induced movement therapy, context-focused therapy, goal-directed/functional training, and/or home programmes for improving motor activities

or self-care function; (4) BoNT, diazepam, or selective dorsal rhizotomy for spasticity management; (5) fitness training for aerobic fitness; (6) pressure care for reducing the risk of ulcers; (7) bisphosphonates for improving bone mineral density; and (8) anticonvulsants for managing seizures. When delivering interventions to children with CP, it is paramount that clinicians choose evidence-based interventions at the activities and participation level that hone the child's strengths and reflect their interests and motivations, and ultimately seek to help children live an inclusive and contented life. However, when choosing interventions at the body structure and functions level, the primary purpose is to mitigate the natural history of CP (such as hip dislocation) and the probable physical decline from secondary impairments,<sup>118</sup> rather than trying to fix the condition. We must also remain mindful that conflicts can arise between what families hope for and what the evidence suggests will be helpful or is realistically possible.<sup>202</sup> Part of being truly family centred is to act as an information resource to the family, which will include honest and open disclosure about prognosis using evidence-based tools to guide these difficult conversations.<sup>203</sup> Similarly, designing services based upon goals set by the family<sup>5,64</sup> is best practice and can also help to set the scene for discussing what is realistic and possible from intervention.



Going forward, systematic and disciplined use of outcome measures within all specialties is required for generating new evidence and confirming treatment effects of commonly used interventions. Routine outcome measurement is especially important when yellow-light interventions are being applied, and could circumnavigate some of the genuine research barriers including low availability of research funds and difficulties in assembling large homogenous samples. This recommendation is particularly vital for the fields of speech pathology, social work, and psychology that provide key services to children with CP, without strong evidence, as of yet, to support their practice. These professions have been overshadowed in the CP research arena until recently, when the field stopped solely redressing physical impairments and started to look further afield to engendering outcomes in well-being and participation. In addition, systematic and disciplined use of outcome measures is also needed when prescribing assistive technology and assistive devices (such as wheelchairs, walking frames, and communication devices) for children with CP, because devices form a large part of standard care. To date, specialized equipment and technology has been vastly under-researched, probably because the benefits are easily observable (such as independent mobility) and the studies are expensive to conduct; however, in light of device abandonment issues and associated costs, extensive efficacy research is warranted at both an individual and a population level. Moreover, prescribing assistive technology with a specialized appearance (such as orthotics, suits, computerized devices, robotics) may well elevate expectations of good outcomes and give rise to an overinflated perception of high-quality expert care. Thus, it is essential to know if the interventions are working, so as to prevent device abandonment, false hopes, and unnecessary effort.

When yellow-light interventions are used, it is imperative that clinicians utilize a sufficiently sensitive outcome measure to confirm whether or not the intervention is working and if it is helping the child achieve their family's goals. The Canadian Occupational Performance Measure (COPM) and Goal Attainment Scaling (GAS)<sup>5,64,204</sup> have been widely adopted in the literature for assessing goal achievement because they are valid, reliable, sensitive to change, and clinically affordable. Moreover, both measures work well within the family-centred approach because they encourage family-led goal setting and facilitate individualization, which is important for such a heterogeneous condition as CP. For yellow-light interventions, in addition to measuring whether goals are achieved, it may be desirable to measure if the intervention is actually achieving what it purports to do for each individual. Systematic individual outcome measurement, conducted at a population level with data aggregation, would introduce the possibility of rapidly expanding the evidence base amongst this heterogeneous population.

Parents, young people, and doctors have identified eight consensus measurement domains, important for assessing the impact of a CP intervention, that span the ICF levels.<sup>205</sup> We identified systematic reviews that provided measurement

recommendations for evaluating these eight domains in a way that was sensitive to change. The first of these eight domains is impairment, which can be subdivided into (1) spasticity, measured using the Modified Tardieu Scale<sup>5,64</sup> and (2) fine motor, measured using the Melbourne Assessment of Unilateral Upper Limb Function<sup>11</sup> and the Quality of Upper Extremity Skills Test.<sup>11</sup> The second domain is general health. Valid and reliable instruments exist regarding general health in the literature, but less is understood about whether these measures are sensitive to change in CP, and therefore no recommendations are made at this juncture. Third is the gross motor skills domain, measured using the Gross Motor Function Measure.<sup>73,206,207</sup> The fourth domain is self-care/fine motor skills, which can be subdivided into (a) self-care, measured using the Paediatric Evaluation of Disability Inventory<sup>206</sup> and the Activities Scale for Kids<sup>207,208</sup> and (b) fine motor, measured using the Assisting Hand Assessment for activities performance measurement.<sup>11</sup> Fifth is the speech/communication domain, measured using GAS.<sup>209</sup> The sixth domain is integration/participation which can be measured using the COPM or GAS<sup>204</sup> (note that other domain-specific measures exist such as the LIFE-H, but this does not have adequate sensitivity to detect change). Finally, regarding both the seventh domain, quality of life, and the eighth domain, caregiver instruments, valid and reliable instruments exist in the literature, but less is understood about whether these measures are sensitive to change, and therefore recommendations for use are not made at this juncture.

In line with the principles of evidence-based care and as a cost-saving measure, it is highly recommended that craniosacral therapy, hip bracing, hyperbaric oxygen, neurodevelopmental therapy, and sensory integration should all be discontinued from CP care. Interestingly, these ineffective interventions for the most part are founded upon out-dated neurological theories about CP. For example, hyperbaric oxygen as a treatment for CP was based on the now disproven assumption that all CP arises from a lack of oxygen during birth (true for only 5–10% of cases<sup>190</sup>) and that increased oxygenation ought to help repair brain function. Neurodevelopmental therapy sought to reduce hyper-reflexia by repositioning the limb on stretch, providing a local pattern-breaking effect mimicking spasticity reduction, but we now know (1) that local effects do not translate to a reduction in centrally driven spasticity long term<sup>210</sup>; and (2) that no substantive evidence exists to support the idea that inhibition of primitive reflex patterns promotes motor development.<sup>12</sup> Likewise, 'bottom-up' approaches, in which children's underlying motor deficits are treated with the aim of preparing them for function (such as neurodevelopmental therapy and sensory integration) were commendable pursuits when originally invented but disappointingly have little carryover into functional activities.<sup>12</sup>

Over a decade ago, CP research experts<sup>12</sup> and systematic review authors called for 'concerted efforts to investigate other therapy approaches that may prove more clearly beneficial'.<sup>142</sup> These therapy experts were referring to

performance-based or 'top-down' approaches based on motor learning theory, in which interventions focus directly on specific task training in activities of interest and are not concerned with underlying impairments in body structures and function.<sup>201</sup> This visionary advice, in concert with the researchers who rigorously tested their theories, has transformed CP rehabilitation in recent years. The majority of the 'do it' or green-light effective CP therapy evidence generated in the last 10 years are in fact top-down therapy approaches, aimed at improving activities performance and inducing neuroplasticity, and include bimanual training, constraint-induced movement therapy, context-focused therapy, goal-directed/functional training, occupational therapy after toxin, and home programmes. Consistent with the theoretical underpinnings, research has not focused on whether these top-down approaches had a positive effect at the body structures and function level of the ICF (Table II).

Given the sudden increase in new effective treatment options available, it is essential that the field widely embraces and implements these interventions in order to ensure that children with CP achieve the best possible outcomes. Adoption of evidence-based practice also involves the difficult task of getting clinicians to stop providing ineffective treatments that they 'love'.<sup>211</sup> It has been suggested that the field requires professionals 'who want to do the best they can for their patients, who are willing to continually question their own managements, and who have readily available sources of information about what does work'.<sup>211</sup> Our present systematic review seeks to provide the CP field with a comprehensive overview about what works for children with CP and what does not (Fig. 4). Based on best available evidence, the challenge now is for the field to stop permissive endorsement of proven ineffective interventions on the basis of perceived low risk and clinical expertise. This recommendation includes ceasing provision of the ever-popular NDT. This is because NDT has been a mainstay physiotherapy and occupational therapy treatment for many years, but for the most part, the evidence base is unfavourable. Of note, contemporary NDT therapists eclectically include additional evidence-based treatment approaches under the NDT banner (e.g. motor learning and the philosophy of family-centred practice), and it is difficult to distil which treatment approaches are being used with fidelity and what features of the treatment are actually working.

Nevertheless, three systematic reviews have been conducted of traditional NDT,<sup>141–143</sup> including 18 discrete RCTs: 15 measuring efficacy and three measuring optimal dose. Of the 15 RCTs measuring NDT efficacy, 12 trials (studying 674 children) found no statistically favourable benefits from NDT; these trials were of varying quality (high, moderate, and low), whereas three trials (studying 38 children) showed improvements in body structures and functions such as gait parameters, spirometry, and milestone acquisition. The three favourable trials were all at high risk of bias when assessed using the Cochrane criteria,

including small sample sizes ( $n < 16$ ) and extremely low methodological quality such as a lack of blinding, intention-to-treat analysis, concealed allocation, etc. In the three NDT dosing RCTs, two studies (studying  $n = 96$  children) found no difference between intense or regular NDT, whereas one more recent study, by Tsorlakis<sup>212</sup> ( $n = 34$ ), showed favourable outcomes from higher-intensity NDT over lower-intensity NDT. The most recent NDT systematic review<sup>143</sup> cited the Tsorlakis<sup>212</sup> RCT as the sole high-level evidence for NDT being favourable, excluding older evidence and thus all the unfavourable NDT RCTs. Since this is not a standard systematic review methodology for providing proof of efficacy, the results of this systematic review<sup>143</sup> should be interpreted with caution. The difference in inclusion criteria between the systematic reviews explains why the newer systematic review<sup>143</sup> suggests a more favourable benefit from NDT than the earlier systematic reviews that concluded ineffectiveness.<sup>141,142</sup>

In order to determine the strength of recommendation, the panel weighed up the balance of benefits and harms from NDT and concluded that there was strong evidence that NDT does not improve contracture and tone, along with weak evidence that NDT does not improve function. This was because, first, when the methodological quality of the evidence base was considered, the highest quality evidence suggested NDT was ineffective, with only low-quality, high risk of bias studies finding a favourable benefit from NDT. Second, the importance of the outcome that NDT aims to prevent was considered: (1) regarding contracture, which is painful and can limit function, high-quality RCTs showed that casting was a superior treatment to NDT for contracture management and therefore the panel favoured casting; (2) regarding tone reduction, the highest quality evidence suggested that NDT was ineffective for this indication and other evidence shows BoNT exists as a highly effective alternative and therefore the panel favoured BoNT or other effective pharmacological agents. Third, the magnitude and precision of treatment effect was considered: only 3 out of 15 trials found any benefit of NDT, and in these studies the treatment effects were small with very low precision estimates as a result of methodological flaws. Fourth, the burdens and costs of the therapy were considered: NDT is time-consuming and expensive for families, and, what is more, a high-quality RCT shows that substantially better functional motor gains are achieved from motor learning than from NDT at equal doses.<sup>213</sup> Therefore, despite the evidence being less well understood for the likelihood of NDT influencing functional motor gains (yellow light), the panel favoured motor learning since superior gains were possible from an equal dose. Furthermore, since no other body structure and function intervention in this review showed gains beyond the body structure and function level up into the activity level, it is hard to imagine why NDT would be the exception to this trend.

In summary, high-quality evidence demonstrates that casting is superior to NDT for managing contracture; BoNT exists as a highly effective alternative to NDT for

managing tone since NDT is ineffective for this indication; and despite less being known about whether NDT improves function, high-quality evidence indicates that motor learning is superior to NDT for improving function. Consequently, there are no circumstances where any of the aims of NDT could not be achieved by a more effective treatment. Thus, on the grounds of wanting to do the best for children with CP, it is hard to rationalize a continued place for traditional NDT within clinical care.

### Recommendations for research

In future, systematic review authors should assign a GRADE to the body of evidence summarized, to enable clinicians to more quickly interpret the findings of the review for clinical practice. For the motor learning interventions that were 'green light', researchers have repeatedly called for future investigations to determine optimal dosing, to better assess the widely held belief that 'more is better'. Understanding optimal intensity of therapy is important for maximizing outcomes, accurately costing services, and offering family-friendly, achievable interventions. For all the green-light interventions, additional studies that evaluate long-term outcomes are necessary. First, because families of children with CP have life-long caregiving responsibilities, an understanding the impact of these time-intensive and expensive interventions would help with expectation management and planning for lifetime care. Second, it is unknown if some interventions continue to add an incremental benefit when used repeatedly over years or whether the gains are one-off and short term only. Long-term outcome data are essential for costing and optimizing the outcomes of children with CP.

For the yellow-light interventions with lower-quality evidence or a paucity of research to support effectiveness, recommendations for research include the use of individual patient meta-analyses to accelerate data aggregation; collaborations that strategize multicentre data collection to overcome sample size barriers; and the use of CP registries and single-system designs if RCTs are deemed impossible or ethically undesirable to conduct. Use of these research methodologies is advisable and appropriate across all disciplines but would have particular value if applied to the disciplines of orthopaedic surgery, speech pathology,<sup>214–216</sup> and social work, in order to better substantiate the important contributions these clinicians make to CP care. The CP field would also benefit from social workers and psychologists confirming the assumed benefits of proven interventions from non-CP populations amongst children with CP.

When the whole evidence base was viewed from a global perspective, there was a startling lack of interventions available to improve children's participation within their community. Given that this has been identified by many of the systematic review authors as a priority area for intervention, more research designed to measure the effects of participation interventions and funds dedicated to this end is urgently needed. Furthermore, until participation-specific measures with sensitivity to change have been

developed, researchers need to measure the effects of participation intervention using GAS or the COPM.

### Study limitations

All systematic reviews are prone to publication bias from the included trial data; therefore, this systematic review of systematic reviews may incorporate this inherent bias. There is also no guarantee that absolutely all relevant systematic reviews were retrieved, despite the thorough search strategy. Publication bias, however, is unlikely to be more of a problem when identifying systematic reviews than when identifying clinical trials. Moreover, conducting a systematic review of systematic reviews is a study limitation in its own right because the method does not create any information that was not already available. Furthermore, using a high-level synthesis helicopter view means that specific intervention details about how the intervention took place, who benefitted from the intervention, and for how long the intervention was carried out for were not reported; clinicians would need to turn to the included papers to obtain this information. In its place we hope that the knowledge synthesis will help to bridge the gap between research and practice by providing comparisons of varying interventions to aid decision making.

### CONCLUSION

In conclusion, we found compelling evidence from systematic reviews to suggest that the following interventions are effective at the body structures and function level alone: anticonvulsants, ankle casting, BoNT, bisphosphonates, diazepam, fitness training, hip surveillance, pressure care, and selective dorsal rhizotomy. We also found compelling evidence from systematic reviews to suggest that the following interventions improve function at the activities level: bimanual training, constraint-induced movement therapy, context-focused therapy, goal-directed/functional training, home programmes, and occupational therapy after BoNT. No interventions were shown to work conclusively at more than one level of the ICF. Therefore, if a body structures and function outcome is desired, the intervention must be selected from the suite of evidence-based body structures and function interventions. Conversely, if an activities-level outcome is sought, top-down learning interventions, acting at the activities level, must be applied.

The lack of certain efficacy evidence for large proportions of the interventions in use within standard care is a problem for people with CP, healthcare providers, purchasers of healthcare, and funders. More research using rigorous designs is urgently needed as CP is the most common physical disability of childhood with a life-long impact.<sup>190</sup>

### SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Table SI:** Search strategy.

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Licensed content author	Catherine Morgan, Iona Novak, Nadia Badawi
Licensed content date	Sep 1, 2013
Volume number	132
Issue number	3
Start page	e735
End page	e746
Type of Use	Dissertation/Thesis
Requestor type	Individual
Format	Print and Electronic
Portion	Full article
Order reference number	None
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Type of use	Dissertation/Thesis
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Title of your thesis / dissertation	Optimising motor learning of infants at high risk of cerebral palsy using environmental and goal oriented interventions
Expected completion date	Jun 2015
Expected size (number of pages)	15
Requestor Location	Catherine Morgan Cerebral Palsy Alliance 187 Allambie Rd Allambie Heights Sydney, Australia 2100 Attn: Catherine Morgan
Billing Type	Invoice
Billing Address	Catherine Morgan Cerebral Palsy Alliance 187 Allambie Rd Allambie Heights Sydney, Australia 2100 Attn: Catherine Morgan

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